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Life Events and Psychosis: Contexts and Mechanisms

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LIFE EVENTS AND PSYCHOSIS: Contexts and Mechanisms

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Abstract

Since the seminal work of Brown and Birley, the potential link between life events and psychosis has been the focus of research and speculation. However, to date, there have been few studies of life events prior to the onset of psychosis; making it impossible to disentangle whether a higher prevalence is a cause or consequence of the disorder. Furthermore, studies have neglected important characteristics, such as severity and type, and rarely considered potential psychological mechanisms. The primary aims of this study were to extend the current literature by investigating the impact of life events and difficulties on the onset of psychosis, and investigate potential synergistic effects and mediating factors. Data on 253 first-presentation cases and 301 population-based controls were drawn from the Childhood Adversity and Psychosis study. Life events and difficulties experienced one year prior to onset (cases) or interview (controls) were assessed with the Life Events and Difficulties Schedule. Potential causal partners included negative schematic beliefs (assessed using the Brief Core Schema Scales) and potential mediators included symptoms of anxiety and depression (assessed using the Hamilton Anxiety and Depression Questionnaires). There was strong evidence that severe and intrusive experiences were particularly associated with psychosis, showing a three- to twelve-fold increase in odds. The impact of severe experiences was found to be cumulative. There was also tentative evidence that low social class and negative self-schemas combined synergistically with these experiences to increase the odds of psychosis. However, there was no evidence of mediation via affective symptoms. The one year period before the initial onset of psychosis is likely to be a time of serious psychosocial stress, potentially characterised by threatening and intrusive experiences. Research must continue to examine potentially modifiable mechanisms that may link such stressors and psychosis in order to improve our understanding and treatment of these disorders.

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List of Abbreviations

ALSPAC	Avon Longitudinal Study of Parents and Children
APA	American Psychiatric Association
BCSS	Brief Core Schema Scales
CAPsy	Childhood Adversity and Psychosis study
CATEGO	Categorical Assessment of Psychiatric Disorder
CBT	Cognitive Behavioural Therapy
CEQ	Cannabis Experiences Questionnaire
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
DSM-IV / DSM-5	Diagnostic and Statistical Manual of Mental Disorders (4 th /5 th edition)
ESeC	European Socio-Economic Classification system
FIGS	Family Interview for Genetic Studies
GAF	Global Assessment of Functioning Scale
HAM-A	Hamilton's Anxiety Scale
HAM-D	Hamilton's Depression Scale
ICD-10 / ICD-11	World Health Organisation's International Classification of Diseases (10 th /11 th edition)
ICR	Interaction Contrast Ratio
IoPPN	Institute of Psychiatry, Psychology & Neuroscience
IQR	Inter-quartile range
LEDS	Life Events and Difficulties Questionnaire
LTE	List of Threatening Experiences
MEL	Munich Interview for the Assessment of Life Events and Conditions
MRC	Medical Research Council
ONS	UK Office of National Statistics
OR	Odds ratio

OPCRIT	Operational Criteria Checklist for Psychotic and Affective Disorders
PAF	Postal Address File
PERI	Psychiatric Epidemiology Research Interview
PLE	Psychotic-like experience
PSE	Present State Examination
PSQ	Psychosis Screening Questionnaire
PTSD	Posttraumatic stress disorder
RSES	Rosenberg Self-Esteem Scale
SCAN	Schedules for Clinical Assessment in Neuropsychiatry.
SD	Standard deviation
SELCoH	Biomedical Research Centre South East London Community Health study
SLaM	South London and Maudsley NHS Foundation Trust
WHO	World Health Organisation

CHAPTER 1 - General Introduction

“It is the psychiatric epidemiologist’s hope that he will discover some link in the causal chain that *can* be broken.” (Robins, 1978: 697)

Synopsis

Schizophrenia and other psychoses are generally considered to be multi-factorial disorders, with many interrelated risk factors. The past decade has seen a renewed interest in the impact of social factors on the aetiology of psychosis (e.g. Cantor-Graae, 2007; van Os, Kenis & Rutten, 2010; Matheson et al., 2011), and stress is one factor that has been consistently included in models of both the development and maintenance of psychotic disorders (e.g. Zubin & Spring, 1977; Nuechterlein et al., 1994). Read, Mosher and Bentall (2013: 4) recently asserted that “the majority of the public, many members of the mental health professions and most people labelled ‘schizophrenic’ understand that mental health difficulties originate in life circumstances – past and present.” It also appears that academics are beginning to be responsive to the possibility of adverse experiences playing a more fundamental role in the onset of psychosis, and the view that biological factors are of sole central importance to the aetiology of this disorder is no longer the dominant position. For instance, recent models of aetiology implicate life events, and their associated cognitions, as playing a key part in onset of psychosis, mainly through their impact on the dopamine system (Howes & Murray, 2014). Due to the fact that the association between life events and psychosis is receiving renewed interest within the academic community, it appears timely to assess this relationship using a more robust design and a more in-depth method than has previously been employed.

In response to the quotation at the beginning of this chapter, it would be foolish to believe that by uncovering a more robust association between adverse life events and psychosis, that these events would then become the sole target of a potentially breakable chain to psychosis. Many life events are an inevitable part of human existence and are unlikely to be preventable. Furthermore, individuals are likely to differ in the way they react to threatening experiences as a result of pre-existing factors and circumstances, and therefore a similar event can affect different individuals in a variety of ways and may not always be detrimental to later health outcomes. Where preventative efforts

could prove to be beneficial is firstly by identifying factors which modify and mediate the life event-psychosis association to increase the risk of disorder, and then focus prevention efforts on these identified variables. It is likely that stressful events are detrimental to mental well-being by impacting on other variables, such as cognitive and affective processes (Garety et al., 2001, 2007), but these assertions are mostly theoretical in nature and therefore the mechanisms involved are largely unsupported by data at this stage. So far, very few researchers have considered the potential psychological factors that may influence the deleterious impact of adverse social experiences. But unlike genotype (at least at present), social environments and the cognitive and psychological reactions they create, can be modified and coping strategies implemented to mitigate the effects of stress, and therefore these represent important avenues for psychiatric research.

The overall objectives of the work presented in this thesis are therefore to explore the associations between adverse life events and difficulties in adulthood and psychosis in an epidemiologically-derived case-control study, and to explore potential psychological pathways which may interact with, and increase the risk of psychosis in those who have been exposed to recent adverse experiences.

This introductory chapter will provide brief summaries of the current understanding of first-episode psychosis and psychotic-like experiences, as well as the definitions used to assess these outcomes in this thesis. It will also cover a brief introduction to life events research and the mechanisms through which negative core schemas and negative affect are purported to influence the risk of developing psychosis, and as before, will define how these variables will be assessed within the thesis. The chapter will conclude with a statement of the aims and an outline of the thesis structure.

1.1. The concept of psychosis

The term psychosis stems from the Greek word ‘ψύχωσις’, which breaks down to ψυχή (psyche-) meaning ‘mind/soul’ and the suffix -ωσις (-osis), which translates as ‘abnormal condition’. The adoption of the term ‘psychosis’ during the first half of the 19th century replaced the old notion of ‘insanity’, and led to much debate on whether there were only one or many forms of this ‘new’ disease (Berrios, 1987). The word ‘psychosis’ was used to distinguish a condition considered a disorder of the mind, as opposed to a ‘neurosis’, which was once considered a disorder of the nervous system (Berrios, 1987).

1.1.1. The history of the concept

The condition now labelled schizophrenia was first described by Emil Kraepelin over a century ago (Kraepelin, [1883], 1981) using the term ‘dementia praecox’ (‘praecox’ meaning early). This label was chosen to signify a progressive and deteriorating illness, where a return to pre-morbid functioning was thought to be unachievable. Some years later, Eugen Bleuler was the first to coin the term ‘schizophrenia’ (a juxtaposition of two Greek words, which literally translate as ‘split mind’) during a lecture at the German Psychiatric Association in Berlin (Bleuler, 1908). Bleuler identified four fundamental symptoms of what he termed the group of schizophrenias – known as ‘the four A’s’: loosening of associations, disturbances of affect, ambivalence and autism (Stotz-Ingenlath, 2000).

Although the terminology and encompassed disorders have seen a number of evolutions since the original 19th century formulations, the fundamental experiences of individuals with psychosis have remained relatively stable (Ross, 2005). Psychotic experiences are likely to include a detachment from reality, which can take the form of delusions, hallucinations and thought disorder (the so called ‘positive symptoms’, indicating the addition of experiences that would not usually be present), as well as ‘negative symptoms’, (indicating an absence of something which would usually be present), which can include a flattening of affect, i.e. a lack of emotional reactivity, and anhedonia - an inability to experience pleasure from previously enjoyed activities (American Psychiatric Association (APA), 2013).

1.1.2. What does it mean to experience psychosis?

Experiences of ‘hallucinations’ can include hearing voices when there is no-one there, or seeing, tasting, smelling or feeling things that other people do not. Experiences of ‘delusions’ include holding strong beliefs that other people around you do not share, and can often have a paranoid or grandiose focus. Individuals with psychosis may also have difficulties with thinking and concentrating, and these experiences can become confusing and overwhelming. Individuals with psychosis may talk in a way that others find difficult to understand and this is sometimes referred to as ‘thought disorder’. As well as experiencing these so called ‘positive symptoms’, people with psychosis may also appear inexpressive, withdrawn or unmotivated. They may find it difficult to find the energy to look after themselves and complete everyday tasks, such as preparing food and getting dressed. These types of experiences are often referred to as ‘negative

symptoms', and therefore form part of the illness profile. However, they can also arise as a result of being overwhelmed by the illness itself, and from feelings of helplessness and depression. They can also be related to unwanted side effects of antipsychotic medication.

It is important to remember that psychotic disorders and experiences of psychosis are vastly heterogeneous and no one person's experiences will be exactly the same as anyone else's. Experiences vary in frequency, intensity, and distress caused and what gets categorised as disorder tends to be at the extreme end of these dimensions of experience. Some people will only experience one of the aforementioned symptoms, whereas others will have several. Some people will experience them only once, others from time to time, and a smaller proportion of individuals will experience them much more frequently. Psychotic experiences can often occur at times of increased stress and are linked to strong emotions and feelings, including anxiety, fear and depression. It can be difficult to separate psychotic experiences from other emotional problems, including depression and anxiety, or from problems resulting from trauma, such as posttraumatic stress disorder or personality disorder. Furthermore, psychotic experiences can also arise due to fever, brain damage, sleep deprivation, when taking certain substances, and when falling asleep and waking up. Therefore, experiences of psychosis can occur in the context of a range of disorders, although the symptoms are likely to share similar neurodevelopmental and psychosocial origins.

1.1.3. Diagnosis and classification of disorder

Currently, the concept of psychosis covers a wide and diverse range of diagnoses, including: schizophrenia, schizotypal disorder, persistent delusional disorders, acute and transient psychotic disorders, induced delusional disorder, schizoaffective disorders, other nonorganic psychotic disorders and unspecified nonorganic psychosis, although the most common psychotic disorder is schizophrenia (International Classification of Diseases (ICD-10), World Health Organisation [WHO], 1992). In addition, psychotic symptoms can also be present in other psychiatric disorders, and can co-occur with depression and mania (Johnson et al., 1991; Dunayevich & Keck, 2000), and somatoform disorders (Simon & Vonkorff, 1991).

Psychotic disorders are "characterised in general by fundamental and characteristic distortions of thinking and perception, and by inappropriate or blunted

affect” (ICD-10, WHO, 1992: 78). Individuals who experience psychotic disorders often show subtle cognitive, social and motor impairments, which are present from an early age (Poulton et al., 2010; Kelleher et al., 2012). As the individual develops, these changes become more noticeable and may take the form of low mood and social withdrawal, before a clear first episode of psychosis has begun (see Figure 1.1. for an overview of the progression of psychosis from childhood to early adulthood, taken from Howes & Murray’s (2014) recent review paper).

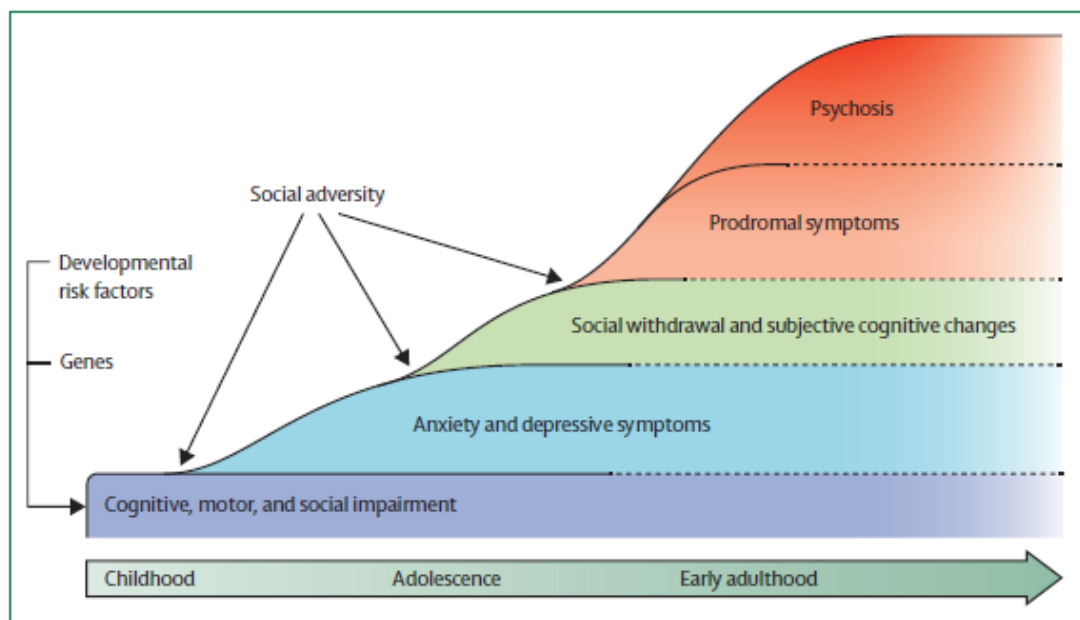


Figure 1.1 The trajectory to schizophrenia showing the evolution of symptoms and the main risk factors (taken from Howes & Murray, 2014)

To receive a diagnosis of schizophrenia using the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), it is necessary to report experiencing at least two characteristic symptoms, which include: delusions (a belief held with strong conviction despite superior evidence to the contrary), hallucinations (the experience of perceptions in any sensory modality in the absence of a real external stimulus), formal thought disorder (disturbance in thought processes, as evidenced by disorganised speech), catatonia and negative symptoms (APA, 2013). A diagnosis of schizophrenia also requires at least one of the two necessary symptoms to be hallucinations, delusions or disorganised speech. Furthermore, symptoms must have been present for at least six months (although this requirement is absent from the ICD-10 criteria), including at least

one month of active symptoms, and show evidence of causing social or occupational dysfunction (APA, 2013).

1.1.4. What underlies the symptoms of psychosis?

As outlined in a contemporary integrated review (Howes & Murray, 2014), the symptoms of schizophrenia and other psychoses are currently thought to arise from neurotransmitter and hormonal abnormalities (e.g. Howes & Kapur, 2009; Stone et al., 2010), neurodevelopmental changes (e.g. Weinberger, 1987; Murray et al., 1992) and biases in cognition and appraisal (e.g. Garety et al., 2001). A brief outline of these three complementary viewpoints will be given below.

The dopamine hypothesis is the most influential and enduring biological theory of schizophrenia (Howes & Kapur, 2009), and attempts to explain the pathogenic mechanisms of the disorder. It arose from the finding that dopamine D2 receptor blockade was a common property of antipsychotic medication and its effectiveness was directly related to affinity for dopamine receptors (Seeman & Lee, 1975). Key features of the current hypothesis are that symptoms of schizophrenia result from either excessive levels of striatal dopamine or excessive postsynaptic receptor sensitivity to dopamine (Howes et al., 2012). Heightened dopamine levels have been proposed to underlie the positive symptoms of schizophrenia, such as hallucinations and delusions, through the attribution of abnormal salience to normal occurrences (Kapur, 2003). Although most of the research into the role of dopamine dysfunction has focused on schizophrenia, it has also been detected in other psychotic disorders (Abi-Dargham et al., 2004), and in individuals with subclinical psychotic experiences (Howes et al., 2011). Interactions between gene variants, including those influencing dopaminergic function, and environmental risk factors are also another possible route to dopaminergic dysfunction, and potential expression of psychotic experiences. This is illustrated by findings of an interaction between single nucleotide polymorphisms (SNPs) in the FK506 binding protein 5 (FKBP5) (hypothesised to be involved in HPA-dysfunction and dopamine abnormalities), and childhood trauma in their effect on psychotic symptoms (Collip et al., 2013).

A neurodevelopmental approach to understanding psychosis is based on three major forms of evidence – pre-and peri-natal complications, developmental delays and brain alterations (Murray & Lewis, 1987; Weinberger, 1987); all of which have shown

links with dopaminergic dysfunction (e.g. Cohen & Servan-Schreiber, 1992; El-Khodori & Boksa, 2003; Slotkin et al., 2006; Howes & Kapur, 2009). Over the past few decades, a large body of literature has accumulated which suggests that obstetric complications, including low birthweight, caesarean section, hypoxia, and other perinatal hazards, are associated with a modest increased risk of schizophrenia in offspring (Clarke et al., 2006), as is prenatal exposure to infection (Khandaker et al., 2013). Evidence suggests that exposure to prenatal (Slotkin et al., 2006) and perinatal stressors (El-Khodori & Boksa, 2003) leads to increases in dopamine release, and that these insults could have additive, or even multiplicative effects that could explain the origin of schizophrenia further down the lifecourse (Howes & Murray, 2014). Individuals who go on to develop schizophrenia in later life have also been shown to have an abnormal developmental trajectory, including motor delays, social alterations and cognitive impairments (Jones et al., 1994; Reichenberg et al., 2009), possibly as a result of earlier obstetric complications and/or prenatal infection. Advancements in neuroimaging techniques have also provided a window into potential pathogenesis, and there is amassing evidence which implicates a variety of structural brain alterations prior to the onset of schizophrenia, including ventricular enlargement, grey matter reductions, and white matter disruption (Lawrie et al., 2001; Pantelis et al., 2003; Ellison-Wright et al., 2008).

Although the dopamine and neurodevelopmental hypotheses provide explanations for the underlying biology of schizophrenia and other psychoses, cognitive theories are also important to help us gain an increased understanding of the nature of psychotic symptoms. In these cognitive models of the positive symptoms of psychosis (e.g. Garety et al., 2001; Bentall et al., 2009), exposure to environmental stress can lead to perceptual disturbances that cannot be readily explained. Pre-existing cognitive biases and appraisal processes may contribute to an explanation that these experiences are externally driven, uncontrollable and potentially threatening. Cognitive models have also been extended to include the role of dopamine, as emphasised by the hypothesis that an increase in dopamine signalling may lead to unusual salience being given to certain stimuli, and the cognitive interpretation of these stimuli (e.g. via negative biases) can lead some individuals to develop psychotic symptoms (Garety et al., 2007; Heinz & Schlagenhauf, 2010). Over time, further stress exposure and additional dopamine dysregulation may lead to paranoid interpretations which are resistant to change (Murray, 2011).

1.1.5. An integrated sociodevelopmental aetiology for psychosis?

According to Howes and Murray's (2014) latest aetiological model of psychosis, the three predominant theories that underlie the symptoms of psychosis (dopamine, neurodevelopmental, cognitive), can be thought to co-exist under one uniting framework. It is now proposed that neurodevelopmental changes due to genetic variation, prenatal and perinatal hazards, and exposure to childhood adversity sensitise the dopamine system in the brain, and can result in increased dopamine synthesis and release. Alongside this, experiences of social adversity can bias an individual's cognitive schema to view themselves and the world around them in a more negative and threatening light. When an individual experiences further stress later down the line (i.e. adult life events), this activates the dopamine system which may cause the misattribution of salience to certain stimuli, and an interpretation based on biased cognitive processes. For some individuals, these experiences can lead to psychotic symptoms such as paranoia and hallucinations, which in turn cause further stress and confusion. The experience of these early symptoms is proposed to lead to a vicious cycle, and the excess strain on the dopamine system can contribute to development of psychotic symptoms that eventually become hardwired and resistant to change (Howes & Murray, 2014).

1.1.6. The epidemiology of psychotic disorder

In terms of the prevalence or lifetime risk of clinically relevant psychosis, this has been estimated to be around 3% (van Os et al., 2009), and for schizophrenia, specifically, lifetime prevalence are lower, with rates of around 0.4% (Saha et al., 2005) to 0.9% (Perala et al., 2007). Moreover, an incidence rate for all psychoses has been estimated at approximately 20 to 30 per 100,000 per year, and for schizophrenia, 15 per 100,000 per year (McGrath, 2007). Estimates of prevalence and incidence can also vary, even within the same country (McGrath et al., 2004; Fearon et al., 2006), and between urban and rural settings, and between the sociocultural majority and minority populations (van Os & McGuffin, 2003). However, these variations can provide some interesting insights into the aetiology of psychosis across different groups and settings.

1.2. First episode psychosis defined for this study

The cases included in the study reported in this thesis are individuals with a first episode psychotic disorder, defined as individuals who present to psychiatric services for the first time with psychotic symptoms that meet criteria for any of the aforementioned diagnostic categories, albeit not limited to any specific diagnoses. Specifically, individuals were included in this study if they fulfilled the criteria for either C *or* D below from the Screening Schedule for Psychosis (Jablensky et al., 1992), and these symptoms had been present for a least one day in duration, with no evidence of an organic cause.

C. At least *one* of the following:

- Hallucinations or pseudo-hallucinations in any modality
- Delusions
- Marked thought and speech disorder (e.g. incoherence, irrelevance, thought blocking, neologisms, incomprehensibility of speech) other than simple retardation or acceleration
- Marked psychomotor disorder (e.g. negativism, mutism or stupor, catatonic excitement, constrained attitudes or unnatural postures maintained for long periods) other than simple retardation or acceleration
- Emergence or marked exacerbation of bizarre and grossly inappropriate behaviour (e.g. talking or giggling to self, acts incomprehensible to others, loss of social constraints etc.)

D. At least *two* of the following:

- Marked reduction or loss of interests, initiative and drive, leading to serious deterioration of the performance of usual activities and tasks
- Emergence or marked exacerbation of social withdrawal (active avoidance of communication with other people)
- Severe excitement, purposeless destructiveness or aggression
- Episodic or persistent states of overwhelming fear or severe anxiety
- Gross and persistent self-neglect

1.2.1. Justification for using a broad definition of psychosis

A broad definition of psychosis was chosen for this study in order to explore the characteristics of a wider group and to ensure information was not lost due to the exclusion of one or more diagnostic categories, e.g. affective psychoses. The distinction between the various diagnostic categories within psychosis has been the subject of much recent debate (e.g. Cardno et al., 2002; Lake & Hurwitz, 2006; Dutta et al., 2007; Kingston et al., 2013), and therefore it was felt that reliance on specific diagnoses when measuring psychosis may well be problematic. The experience of psychotic symptoms has been linked to numerous psychiatric disorders, as well as medical conditions such as Lyme's disease (Fallon & Nields, 1994), and syphilis (Rundell & Wise, 1985), and substance abuse (Tien & Anthony, 1990). Furthermore, at first presentation, the clinical picture can be uncertain and diagnosis is often not clear and can be unreliable. This is illustrated by a recent study which found that only 59.6% of an incident first-episode sample were found to have the same baseline and lifetime ICD-10 diagnosis at a ten year follow-up review (Heslin et al., submitted). These findings suggest that diagnoses at first-episode should be considered provisional. Therefore, given this likely instability, and the heterogeneity of psychosis and its associated diagnoses, there is an increasing trend to focus on specific symptoms when exploring aetiology (e.g. Bentall, 2003; van Os & Kapur, 2009; Waddington et al., 2012). An individual symptom approach influenced the way psychosis was defined for this thesis, whereby individuals were eligible for inclusion if they presented to psychiatric services for the first time with evidence of psychotic symptoms, regardless of their diagnosis. It was felt that beginning from this widest starting point makes most scientific sense in this first-presentation sample.

Moreover, using a sample of first presentation patients is advantageous in that it reduces the influence of potential confounders, including chronic illness, long-term use of anti-psychotics, institutionalisation, and deteriorations in memory and cognitive functioning. Furthermore, restricting the design to focus solely on new incident cases of disease, rather than prevalent cases, or a combination of the two, reduces the possibility of recruiting a sample which has an over-representation of cases with long-standing symptoms and a potentially poor prognosis. When wanting to tease apart potential causal relationships and gain a better understanding of aetiology, a sample of incident cases is more suitable as the risk factors under study are more likely to be associated with the onset of disorder, rather than a poor prognosis (Lewis & Pelosi, 1990).

1.3. Psychotic experiences within the general population

Over the past few years, numerous studies have shown that psychotic experiences, defined narrowly as low level (i.e., infrequent, low intensity, non-distressing) hallucinations and delusions, are common in the general population and may represent evidence of a continuum model (e.g. Kendler et al., 1996; Poulton et al., 2000; van Os et al., 2000, 2009). This phenomenological continuum is proposed to encompass normal experiences and normal expressions of personality at one end, and psychotic disorder at the other. These findings imply that the same symptoms seen in patients with psychotic disorders can also be measured in non-clinical populations, and that experiencing symptoms such as delusions and hallucinations is not inevitably linked to the presence of a clinical disorder. Viewing psychosis within a continuum framework has allowed researchers to further understand the variation in the severity of psychotic experiences, recognise that individuals may exist at a fixed point along the continuum (either fleetingly or more long-term), and to consider trajectories of experiences across time, from subclinical to experiences which are clinically-relevant and with a need for treatment (Murphy et al., 2012).

When the psychosis phenotype is expressed at levels below clinical diagnosis, this has been commonly referred to as psychotic experiences (van Os et al., 2000; Stefanis et al., 2002), psychotic proneness (Chapman et al., 1994), schizotypy (Meehl, 1962), and at-risk mental states (Yung et al., 2003). Some researchers have drawn a meaningful distinction between clinically-relevant ‘psychotic symptoms’ which do not meet the threshold for psychotic disorder, and subclinical ‘psychotic experiences’ (van Os et al., 2009). Help-seeking, level of distress and a need for care are obvious distinctions between those who present at clinical high-risk services and those with psychotic experiences in the general population. Environmental exposures, such as adult life events and difficulties, may also cause psychotic experiences to persist as the proneness-persistence-impairment model of psychotic disorder (van Os et al., 2009) suggests that exposure to stress may influence the distress and impairment associated with psychotic experiences, and this may confer a greater risk for psychotic disorder (van Os et al., 2010). However, the factors which influence the transition from low-level or non-distressing psychotic experiences to those which require intervention and intensive support still need to be more thoroughly investigated (Kaymaz & van Os, 2010).

1.3.1. The epidemiology of psychotic experiences

The presence of psychotic experiences within the general population has been found to have a reported lifetime prevalence ranging from 2% to 28% (van Os et al., 2009). This is much higher than for clinically significant psychotic disorder, which has been reported to affect between 1% to 4% of the population (van Os et al., 2000; Shevlin et al., 2007), and these differences in prevalence provide support for a phenomenological continuum model of psychosis (van Os et al., 2009). However, the van Os paper (2009) suggests that there is heterogeneity in the prevalence of psychotic experiences, and much of this can be attributed to study cohort and design factors (Linscott & van Os, 2010).

The validity of this extended phenotype has been well demonstrated. For example, psychotic experiences have also been shown to be associated with the same risk factors that influence clinical psychosis, such as urbanicity, ethnic minority status and younger age (Verdoux et al., 1998; van Os et al., 2000; Morgan et al., 2009), and therefore may represent an important group from which to gain aetiological advances. Validity is also enhanced through the findings that individuals who report psychotic experiences are at an increased risk of developing a later psychotic disorder. In the Dunedin longitudinal cohort study, Fisher et al. (2013b) found that the report of psychotic experiences at age 11 was associated with around a 7-fold increased risk of schizophrenia at age 38. A recent meta-analysis also estimated the conversion rate of adolescents and young adults considered at clinical high risk for psychosis to range from 22-36% (Fusar-Poli et al., 2012). Therefore, these findings make a strong case for using psychotic experiences as a subclinical phenotype to provide further insights into the origin of schizophrenia and other psychotic disorders (Kelleher & Cannon, 2011), and may also form a group to target for preventative interventions (Morrison et al., 2004).

However, it is also important to note that there is a large degree of non-specificity and that associations have also been found between early psychotic experiences and other psychiatric disorders such as anxiety (Poulton et al., 2000). In the Fisher et al. (2013b) study, those who reported psychotic symptoms in childhood were more likely to receive a diagnosis of PTSD, and attempt or complete suicide by age 38 than those who did not report psychotic experiences. Associations were also found between early psychotic experiences and a range of other psychiatric outcomes in later adulthood, including anxiety, depression and substance dependence, albeit weaker than

those found for psychotic disorder (Fisher et al., 2013b). Although psychotic experiences may still provide a valid population for studying the aetiology of psychosis, the report of psychotic experiences should perhaps be better regarded as a non-specific marker for later mental health problems (Murray & Jones, 2012). Some psychotic experiences will be associated with serious clinical disorders, whereas others will not.

1.3.2. Issues surrounding the measurement of psychotic experiences

One important limitation of the research into psychotic experiences in the general population has been a lack of consistency in defining what is considered to be evidence of a psychotic experience (van Os et al., 2009). Research studies have used a vast array of different assessment tools and definitions which makes comparability across studies very problematic. Psychotic experiences have been defined as possible or probable or definite, and these phenomena have been elicited via self-report questionnaires, and clinician-rated and lay person interviews (Laurens et al., 2007; Horwood et al., 2008). There are also issues surrounding the period of interest, and a tool which assesses the presence of lifetime psychotic experiences may give higher estimates than one which enquires about a fixed time point, e.g. one year, and may also be more subject to recall bias.

Although originally designed as a screening tool for psychosis, the Psychosis Screening Questionnaire (PSQ, Bebbington & Nayani, 1995) has now been widely used to measure the report of psychotic experiences within the last year in a number of large-scale population studies (Jenkins et al., 1997a; 2012; Morgan et al., 2009; Das-Munshi et al., 2012). When the PSQ has been used to measure psychotic experiences, rather than as a clinical screening tool, the research findings have been consistent with other psychosis studies (Johns et al., 2004; Morgan et al., 2009), and those endorsing these experiences have been shown to be similar to those identified using clinical instruments (Johns et al., 2002). However, there are a number of limitations to using the PSQ as a measure of psychotic experiences (King et al., 2005). As the PSQ does not take the context into account in which the respondent's endorse specific items, it is likely that this tool will overestimate the prevalence of psychotic experiences (Morgan et al., 2009). It is also important to note that there will be some degree of ambiguity when it comes to interpreting the PSQ questions, and this could lead to misclassification. This could be particularly problematic where certain groups may respond positively to an

item due to their cultural practices. However, similar findings have been reported across different ethnic groups (Johns et al., 2004; King et al., 2005; Morgan et al., 2009). These limitations notwithstanding, the use of the PSQ to measure psychotic experiences within the general population appears to be a justified approach in this thesis, although any findings must be considered in light of these and other limitations.

1.3.3. Psychotic-like experiences (PLE) defined for this study

Controls were assessed for the presence of subclinical PLE within the last year using the Psychosis Screening Questionnaire (PSQ, Bebbington & Nayani, 1995), a structured questionnaire which assesses psychotic experiences across five domains: hypomania, thought disorder, paranoia, strange experiences and hallucinations. Controls who reported one or more psychotic experience(s) within the past year (determined by the endorsement of at least one probe plus follow-up questions), were analysed as part of the subclinical group. The methods used to interpret and report psychotic experiences using the PSQ replicated those previously used by Johns et al. (2004), Wiles et al. (2006) and Morgan et al. (2009), i.e. participants must answer ‘yes’ to all questions within a symptom category (both probe and follow-up questions), with the exception of the paranoia category where endorsement of the first follow-up question (and not necessarily the second follow-up question) was taken as evidence of a psychotic experience. This method is preferred as the second follow-up question in the paranoia category relates specifically to delusions of conspiracy, and therefore may lead to the exclusion of other forms of paranoia.

1.4. Introduction to social risk factors for psychosis

1.4.1. Genes vs Environment

For many years, the aetiology of schizophrenia was considered to be largely driven by genetic factors because of the findings of a roughly uniform incidence across the world (Murphy, 1976). This viewpoint was supported by Tim Crow (2000), amongst others, and suggested that the incidence is apparently unrelated to geographic or other environmental variation. Furthermore, a large WHO study of ten different countries (Jablensky et al., 1992) did not find statistically significant geographical variations in

the incidence of narrowly defined schizophrenia. These findings supported the idea that genetic factors had a key role to play, and the usual variability that would be expected if the occurrence of schizophrenia was influenced by local social environments was simply not evident.

However, more recent studies have challenged this interpretation. In a comprehensive meta-analysis of 100 incident studies, McGrath et al. (2004) found considerable geographic and ethnic variation in psychotic disorders across studies. The variation in the incident rates across sites was more than five-fold, ranging from roughly 7.7 to 43 per 100,000. The meta-analysis also revealed higher rates of psychosis in men, urban centres and in migrant groups (McGrath et al., 2004). Although this uneven epidemiological terrain does not itself point towards a particular aetiology, it does awaken the idea that, aside from a strong genetic component, environmental factors are also likely to play some part in the development of psychotic disorder (McGrath, 2007). This is supported by twin studies that report concordance rates of schizophrenia between genetically identical (monozygotic) twins as less than 50% (Cardno et al., 1999), thus indicating a role for both genetic and environmental factors in the aetiology of this disorder. Rather than acting in isolation from each other, it is perhaps more likely that there is an interaction between genes and the environment in the development of psychosis (Uher, 2014).

1.4.2. A brief overview of social causation

Over a number of decades, evidence has accumulated which suggests that the origin of psychosis has a social component. Two predominant theories focus on the social determinants of health and illness (Thoits, 1999). The ‘structural strain theory’ locates the origins of disorder in the organisation of society. Structural factors (e.g., position within social hierarchies; characteristics of the wider social environment) such as migration, ethnicity and urbanicity have all been implicated in the aetiology of psychosis. These broader structural concepts are also thought to overlap with the ‘social stress theory’, which proposes the origins of disorder to be influenced by social stressors (i.e., individual level and interpersonal experiences). In relation to the development of psychosis, and other mental illnesses, this can include the experience of adversity and trauma in childhood and adulthood.

Migration & Ethnicity

Since the pioneering studies by Odegard (1932) which found first-admission rates for schizophrenia to be high among Norwegian migrants to the United States, the association between migrant status and psychosis has been the subject of much attention. The most comprehensive literature is on people of black Caribbean origin who migrated to the UK, mainly in the 1940s and 50s (Harrison, 1990; Fearon & Morgan, 2006). The AESOP study conducted in south London estimated rates of psychosis to be around seven times higher for the black Caribbean population, and also around four times higher for the black African population than for those who were white British (Fearon et al., 2006). Furthermore, Cantor-Graae and Selton's (2005) meta-analysis demonstrated an increased risk of schizophrenia in all migrant groups. However, associations were found to be strongest for migrants from developing countries who migrated to developed countries, and in those migrating from areas where the majority of the population was black (Cantor-Graae & Selton, 2005). Moreover, the authors showed that not only were first-generation migrants at increased risk, but that in fact their children, the second-generation migrants, were at even higher risk (Cantor-Graae & Selton, 2005).

So why are rates of psychosis higher in migrants and ethnic minority groups? Research suggests that migrants to the UK do not come from places with particularly high rates of psychosis (e.g. Bhugra et al., 1996; Mahy et al., 1999), and therefore the explanation is likely to lie in the social experiences and conditions of being a migrant or belonging to an ethnic minority group. Modood et al. (1997) have shown that non-white groups in the UK, particularly those of African or Caribbean descent endure substantially more social adversity than their white counterparts and are more likely to be unemployed, live in poorer housing, do worse academically and are more likely to be excluded from school. The persistence of these disparities has been attributed to racial discrimination, and experiences of racism are likely to negatively bias an individual's beliefs about themselves and the world around them, which can then increase susceptibility to psychosis (Janssen et al., 2003; Karlsen et al., 2005). Another overlapping explanation is that the majority of the black African and Caribbean population in the UK live in urban environments (ONS, 2012), and this may be independently important in the increased risk of psychosis in these populations, as will be further elaborated below.

Urbanicity

Since the early work of Faris and Dunham (1939), many research studies have found huge variance in the rates of mental illness according to place of residence, particularly those districts characterised by social disorganisation, squalid housing, poverty and excess crime rates, i.e. those in the inner urban zones (Krabbendam & van Os, 2005). The urbanicity effect is particularly strong for schizophrenia and, in a study in Denmark, Pedersen and Mortensen (2001) found that compared with those who had always lived in the most rural areas, the relative risk of schizophrenia for those who had spent their childhood in the capital, Copenhagen, was nearly three times greater. In a meta-analysis of more recent studies, Krabbendam and van Os (2005) estimated that urbanicity accounts for a large proportion of schizophrenia cases – approximately 30%, assuming causality, in Western countries. In terms of explaining why rates of psychosis are higher in those who have been brought up in urban environments, current hypotheses revolve around the overlapping theories of social deprivation (Kirkbride et al., 2007), social capital (Putnam, 2001; Lofors & Sundquist, 2007), social fragmentation (Allardyce et al., 2005), and social integration, e.g. ethnic density (Bosqui et al., 2014).

A key role for life events?

It is clear that certain structural stressors, including migration, ethnicity and urbanicity, are associated with an increased risk of psychosis. These factors are likely to work in concert to increase rates of psychosis, and therefore exposure to cumulative social adversity is likely to be important. A common factor linking these stressors to psychosis is the life events and difficulties that may emerge from these situations. For example, the process of migration is a major life event in itself and events involving racism and discrimination may explain some of the relationship between ethnicity and psychosis. Furthermore, urbanicity may be associated with psychosis via a number of key events and difficulties. Those living in an urban environment may be more likely to be exposed to crime and victimisation events, competition for employment is undoubtedly higher and chronic difficulties such as lack of adequate housing, pollution, and social fragmentation may be more apparent in cities compared to more rural environments. While our understanding of aetiology has certainly improved by studying these structural concepts, using urbanicity, for example, as a broad marker of social adversity can be argued to be fairly crude and difficult to interpret (March et al., 2008). One way

to further understand the nature of the relationship between urban living and psychosis is to draw upon insights and methodologies from the social sciences, and use a detailed interview, such as the Life Events and Difficulties Schedule (Brown & Harris, 1989a), which allow adverse social contexts and experiences to be more fully characterised, and have rarely been used to investigate this model. By identifying the relevant life events and difficulties which are associated with an increased risk of psychosis, we can potentially identify the experiences of living in cities which are detrimental to some individual's mental health. Exposure to certain stressful life events and difficulties can impair an individual's capacity to cope or adapt, thereby leaving them vulnerable to illness. However, in contrast to childhood or more long-term social adversity, the literature about the impact of *recent* life events and difficulties is scarcer, and therefore the focus of this thesis is to attempt to complete this gap.

1.5. Life Events

1.5.1. History of life events research

For many years, life events have been implicated in the onset, course, relapse and outcome of various mental disorders. Life events are characterised as situations or occurrences that bring about a positive or negative change in personal circumstances and/or involve an element of threat. Investigations into life events and mental illness gained a surge of interest in the early 1970s, with studies exploring how social factors influence the onset and course of unipolar depression (Dohrenwend & Dohrenwend, 1974; Brown & Harris, 1978). Since then, and after some forty years of investigating the role of life events and difficulties, the work of Brown, Harris and their colleagues has consistently supported associations between life events and a host of physical and psychiatric illnesses, including depression, schizophrenia and myocardial infarction (Harris, 2000). Furthermore, their research has not only shed invaluable light on the aetiology of a whole host of conditions, their methods are widely recognised as the gold-standard by other prominent researchers in the field (Harris, 2000).

Specificity of life events and mental illness

While confirming basic relationships between life events and mental illness, researchers have also shown evidence of specificity, i.e. that certain life experiences may confer more risk for certain symptoms. In terms of depression, events involving loss, entrapment and humiliation have been found to influence onset (Brown & Harris, 1978). Exposure to danger events have shown associations with anxiety disorders (e.g. Finlay-Jones & Brown, 1981), whereas goal-attainment events may trigger manic symptoms (Johnson, 2005). In terms of psychotic disorders, exposure to intrusive events is thought to have some specificity (Harris, 1987; Day, 1989; Harris, 1991),

1.5.2. Brief overview of life events and psychosis

In terms of the impact of life events on psychosis specifically, it has also long been suggested that patients with schizophrenia are sensitive to the effects of adverse (or negative) life events (Brown & Birley, 1968), but despite an interest which spans almost forty years of research, a clear consensus has yet to emerge (Beards et al., 2013). Researchers have implicated life events in triggering the emergence and recurrence of psychotic symptoms (e.g. Day et al., 1987; Norman & Malla, 1993a; Pallanti et al., 1997; Hultman et al., 1997). However, other researchers (e.g. Canton & Fraccon, 1985; Malla et al., 1990; Bebbington et al., 1993; Hirsch et al., 1996) suggest that life events do not directly trigger a relapse or onset of psychosis, but rather contribute to a cumulatively increasing risk with each subsequent exposure.

The important work of Brown and Birley (1968) prompted some researchers to look beyond the mere presence of life events in the aetiology of mental disorders and investigate other characteristics of events such as independence (i.e. whether the occurrence of an event is potentially influenced by the hypothetical presence of disorder or not), severity and type. In a review of the literature, Norman and Malla (1993a) concluded that there was evidence of a dose-response relationship between the number of events and an increase in psychotic symptoms as the majority of studies assessed showed positive associations between the frequency of recent life events and poorer symptom outcome. It is also likely that event severity will have a differential impact on risk of illness. Symptoms of mental disorder are more likely to be brought about by severe events and this may affect first episodes more than later ones (Canton & Fraccon, 1985; Bebbington et al., 1993; Raune et al., 2009). Patients with a long-standing disorder may become more sensitised as their illness progresses and so relapse may be

less associated with stress. It may therefore be that the association of severe events with psychosis is strongest in relation to onset; an effect which has been demonstrated for patients with depression (Brilman & Ormel, 2001) and bipolar disorder (Ghaziuddin et al., 1990; Post, 1992).

It is important to establish the role of life events in the onset of the disorder and try to illuminate factors that could be tackled to prevent the development of psychosis and encourage more effective initial intervention. In other words, establishing an evidence-based association between adult life events and psychosis could highlight a pathway to disorder and lead to valuable opportunities for prevention and management. However, in its present state, the life events and psychosis literature is flawed by a host of methodological limitations. The majority of studies identified have used relatively small, heterogeneous or unrepresentative samples, and have also lacked suitable control groups, rarely controlled for relevant confounders, and obtained reports of recent life events and psychosis with inadequate assessment tools (Beards et al., 2013). Given the limited evidence available, it is not possible to draw any firm conclusions from existing findings about the association between recent life events and the onset of psychosis and subclinical experiences. A review of the present literature highlights the need for more scientifically rigorous studies that attempt to overcome some of the previous biases and methodological shortcomings (Beards et al., 2013).

1.5.3. Recent life events and psychotic experiences

Similarly to patients with psychotic disorder, an association has been found between exposure to recent life events and the later expression of psychotic experiences within the general population. Johns et al. (2004) found reports of recent life events to be independently associated with psychotic experiences in the past year and Jenkins et al. (2010) found significantly higher rates of such experiences in those who had recently experienced two or more life events in an urban setting in Tanzania. Most recently, van Nierop et al. (2012) found that individuals who experienced negative life events in the previous year were around two times more likely to have experienced at least one lifetime psychotic experience compared with those who did not report any recent adversity.

1.5.4. Alternative explanations

Reverse causality

Assuming a causal relationship between life events and psychosis has been criticised because of the possibility that some events could occur due to the insidious onset of disorder. As schizophrenia and other psychoses are often preceded by a period of functional decline, often leading to major life events and difficulties such as breakdowns in social relationships and employment opportunities, it is extremely difficult to determine the causal direction of any association between markers of social adversity and psychosis. Therefore, it could be argued that certain life events occur as a result of pre-existing symptoms, and are not responsible for increasing the risk for onset. One way of clarifying the potential causal relationship between life events and illness onset is to distinguish between events that are ‘independent’ of emerging symptoms, e.g. death of a close relative, from those which may be influenced by a deteriorating mental state in the period leading up to onset – ‘possibly dependent’, e.g. interpersonal conflict. Research has found that even when ‘independent’ events are considered, there does appear to be an association with psychosis (Brown & Birley, 1968; Bebbington et al., 1993; Faravelli et al., 2007; Raune et al., 2009).

However, it is likely that there will be associations found for both ‘independent’ and ‘possibly dependent’ experiences and the onset of psychosis is likely to be triggered both by the experience of severe events that are completely outside of an individual’s control, but also that individuals susceptible to psychosis may generate an increased amount of life stress. It is not simply that events are either a cause or consequence of (emerging) psychosis; each may compound the other, creating a vicious circle that, over time, pushes some along pathways to later psychotic disorder. Although it may be helpful to assess independence in a bid to understand possible causation and direction of effect, it is perhaps more pertinent to understand the role of possibly dependent experiences if we want to improve preventative efforts. Exposure to independent experiences cannot be controlled, but the way that individuals contribute to the occurrence of certain events and difficulties, as well as the way they react to them, is something that can be studied in order to improve later health outcomes.

Genes as a confounder?

A central assumption of much of the life events literature is that the occurrence of events is mostly or totally random (Fergusson & Horwood, 1987). However, research suggests that genes can influence exposure to life events as well as onset of psychosis and may therefore provide an alternative explanation for an association between life events and psychosis. Using a general population sample of young adults, Breslau et al. (1991) found that exposure to traumatic events was associated with a family history of psychiatric illness. Twin studies also highlight a significant role for genetics in the relationship between life events and mental illness, and research has found that experience of life events is significantly correlated in twin pairs, and these correlations are greater for genetically identical (monozygotic) than for non-identical (dizygotic) twins (Plomin et al., 1990; Kendler et al., 1993). More recently, there have been several studies which suggest an interaction between certain genes and recent stressful events in individuals with psychosis (e.g. Peerbooms et al., 2012; Ira et al., 2014; Pishva et al., 2014). Although these findings suggest that genes may have a significant influence on the relationship between life events and psychosis, research suggests that genetic factors only account for around 20% of the variance in the reporting of life events (Kendler et al., 1993), and so other environmental factors must also play a role.

It is important to note that the likely relationship between genes, life events and illness is a complicated one. Researchers are not implying that genes ‘code’ for life events in the same way as they do eye colour. However, genes are likely to influence certain traits, such as inherited personality characteristics, including impulsiveness, risk taking and stability, and these may increase the probability of experiencing adverse life events (Eaves et al., 1989). When assessing the interplay between genes and environment, there are at least two major pathways to consider (Kendler & Eaves, 1986). The first is a potential ‘gene x environment correlation’ – where genes that influence a trait or disorder also influence the likelihood of exposure to an environment, e.g. genetics influencing the likelihood of an individual choosing to indulge in a high-risk environment. In contrast, a ‘gene x environment interaction’ occurs when the effects of an environmental risk factor, e.g. life events, are moderated by genetic predisposition, e.g. a polymorphism in a particular gene such as the serotonin transporter gene (Caspi et al., 2003).

Both of these pathways imply that genetics may explain some of the relationship between life events and psychosis. The effects of genes and environment are unlikely to act independently and a consideration of the role of genetics, either indirectly through

the assessment of family history, or directly via an assessment of specific genes or regions, is crucial to understanding the potential relationship between life events and the onset of psychosis. Although the thesis will control for family history when looking at the relationship between life events and psychosis, there is not the scope to consider the role of genetics on this relationship and it remains an important area for future research.

1.5.5. Measurement of life events

In the study of life events, there have been two distinct strategies for eliciting the experiences of research participants. The first of these originated in the work of Holmes and Rahe (1967), and consists of a fixed inventory of events that is presented to participants (Tennant & Andrews, 1976). The alternative, developed by Brown and Harris (1978), and the procedure used in this thesis, involves a semi-structured interview with probing questions designed to elicit and rate a diverse range of life events. The Life Events and Difficulties Schedule (LEDS; Brown & Harris, 1989a) was developed to address some of the methodological weaknesses which characterised life events research prior to its creation; namely, no clear determination of the time sequence of events in relation to onset of disorder, no adjustment for the possible effects of the participant's illness on the way they report events, and no way of measuring whether the events are likely to be brought about by the symptoms of the illness under study. The development of the LEDS (Brown & Harris, 1989a) allowed the interviewer to examine the context of the event and to rate the likely meaning using an objective process based on the average person's interpretation if they were facing a similar situation. This approach minimises the potential influence of mood and other symptoms on the severity and other characteristics of the reported events. Furthermore, the inclusion of an 'independence' rating allows the rater to distinguish between events which are unlikely to be the result of the disorder under study because their source was clearly 'independent' of the subject's agency (and therefore necessarily of any hypothetical developing symptomatology). The LEDS method (Brown & Harris, 1989a) also increases the likelihood that events of aetiological significance are identified as there is no limit to the events that could be considered as relevant.

1.5.6. Life events defined for this study

Life events are defined as situations or occurrences that involve a discrete, observable and significant change in personal circumstances (Castine et al., 1998), and/or involve an element of threat. For the purposes of this thesis, the LEDS (Brown & Harris, 1989a) was used to enquire about eleven broad categories of life events and difficulties that occurred to either the participant themselves or to those in their immediate social network, across the one year period prior to onset (cases) or interview (controls). As described before, events are discrete occurrences that bring about a positive or negative change in personal circumstances and/or involve an element of threat, and difficulties are defined as problematic situations that last for a minimum of four weeks. The eleven broad categories and the possible events and difficulties within these categories are outlined as follows (note that this list is not exhaustive):

- **Education** (including: selection interviews; starting or leaving school, university, courses; exams and results; other crises [excluding conduct problems & referrals])
- **Work** (including: job interviews and rejections; starting a job - either starting work for the first time, beginning a new job or resuming work after a period of absence; time off sick or for maternity; strikes lasting for more than four weeks; promotion, demotion, structural change or problem at work; work relationship crises; redundancy or dismissal; retirement or giving up work; contact with a solicitor, court or tribunal regarding work issues)
- **Reproduction** (to be used to classify events up to two weeks after birth) (including: infertility; pregnancy and any complications with pregnancy; miscarriage; induced abortion; birth; stillbirth; contraception; sterilisation)
- **Housing** (including: rent payment and threat of eviction; rented housing event; buying or selling a house; a change of residence; other crises, e.g. with neighbours)
- **Money/Possessions** (including: financial crises and debts; significant financial gains; loss of finances and possessions; damage or threat to property [excluding theft]; financial obligation; solicitor contact regarding possessions)
- **Crime/Legal** (including: an offence against the person, e.g. mugging, rape, assault; offence against property, e.g. theft, burglary, vandalism; other offence, e.g. drugs, driving; any police contact; court case, inquest, prison [including the participant's release]; solicitor contact)

- **Health/Treatment/Accidents** (including: accidents and accidents requiring a hospital stay; physical illness and hospital stay for a physical illness; operations; suicide attempts; psychology referral, problems with substance misuse, child guidance, psychiatric disorder; hospital discharge; solicitor contact regarding health)
- **Marital/Partner Relationship** (including: first sexual intercourse; the start of a new or resumption of a relationship; participant's engagement or marriage; start of cohabitation; an increase or decrease in interaction; crisis or breakdown in relationship; violence or rape from partner; separation or divorce; solicitor contact regarding divorce or custody)
- **Other Relationships, including Children** (including: an increase or decrease in interaction; an arrival or departure from the household; the engagement, marriage, divorce of close other; issues with child conduct, truancy or delinquency; a crisis or breakdown in a relationship; the breaking of bad news to a close tie; violence or pestering by a relative or key tie; contact with police, solicitor or social worker regarding issues with children or close ties)
- **Miscellaneous, including Pet events** (including: meeting a key person or learning a key fact about the past; breaking bad news to a less close tie; ceremonies; pet events; other miscellaneous crises)
- **Death**

As well as classifying the type of event or difficulty, information was also gained about the start date of the event or difficulty and end date for difficulties, duration of difficulties, focus, independence, short-term and long-term severity, and intrusiveness. Full descriptions of these further characteristics are provided in Chapter 4 (Methodology).

1.6. Pathways from life events to psychosis?

Over recent years, there has been a resurgence of interest in the potential role of social factors in the development of psychosis, and this work has been given further impetus by the proposition of a number of plausible biological mechanisms. These proposed mechanisms which link experiences of stress and adversity to an increased risk of psychosis include gene x environment interactions (van Os et al., 2008),

sensitisation of the dopamine system (Collip et al., 2008; Howes & Kapur, 2009), and stress induced dysregulation of the HPA-axis (Walker & Diforio, 1997; Mondelli et al., 2010). Although these suggestions can account for the underlying biological changes in individuals who develop psychosis, there are also a broader range of psychosocial mechanisms that are likely to be relevant. Cognitive and affective factors can play an important role in our judgement making and interpretation of life events, and therefore can lead to an increased risk for psychosis.

A contemporary viewpoint is to consider a more integrative approach which proposes a central role for socio-cognitive factors, but also takes into account newer neurobiological findings (e.g. Broome et al., 2005; Selten & Cantor-Graae, 2005; van der Gaag, 2006; Garety et al., 2007). An example of an integrative theory which brings together biological and social explanations in one uniting theory is that of ‘social defeat’ (Selten & Cantor-Graae, 2005). Drawing on evidence from animal studies, Selten and Cantor-Graae (2005) proposed that experiences of chronic discrimination and social isolation, so called ‘social defeat’ can lead to dopaminergic hyperactivity in the mesocorticolimbic system which increases the risk of developing psychotic symptoms. The authors theorised that this explanation may explain the strong association between migrant status and psychosis, with this group undoubtedly facing more discriminatory and isolative life events and difficulties than their native counterparts (Selten & Cantor-Graae, 2005). Other authors propose that while biological factors such as familial liability or developmental insults put an individual at increased risk for psychosis, it is the biased cognitive appraisals, born out of adverse life events, which will propel an individual into full-blown psychosis (Broome et al., 2005). These socio-cognitive and emotional processes are clearly a vital component in the aetiology of psychosis and their role will be further elaborated below.

1.6.1. Cognitive and affective pathways to psychosis

Various indirect pathways have been proposed from adverse social experiences to psychosis, and have been discussed within contemporary aetiological models of psychosis (e.g. Morgan et al., 2010; van Os et al., 2010; Howes & Murray, 2014), as well as the more psychologically orientated cognitive models of psychosis (e.g. Fowler, 2000; Bentall et al., 2001; Garety et al., 2001, 2007; Morrison, 2001; Freeman et al., 2002). Repeated exposure to social adversity may be associated with psychosis through

the generation of cognitive biases and affective states that predispose individuals to certain symptoms. It should be noted that this thesis will only explore the specific role of negative schematic beliefs and affective symptoms in explaining the relationship between life events and psychosis, due to limitations of data availability. However, in order to set the scene, a brief overview of some of these potential mechanisms, including specific reasoning biases, such as jumping to conclusions and theory of mind, negative schematic beliefs, and also the role of affective processes will be outlined below.

Reasoning biases

Reasoning biases have long been proposed to be associated with psychosis, and two reasoning biases in particular have been highlighted to be strongly associated with delusional beliefs – jumping to conclusions and deficits in theory of mind (Garety & Freeman, 1999). Garety and colleagues have gathered persuasive evidence that a specific bias – ‘jumping to conclusions’ (JTC) may play a major role in this disorder (Garety & Freeman, 2013). JTC can be described as a tendency to reach a conclusion on the basis of limited evidence, and without a thorough consideration of alternative hypotheses. It is most commonly assessed using a probabilistic reasoning task- the ‘beads task’, and a meta-analysis has confirmed that JTC is a characteristic of individuals with delusions (Fine et al., 2007). Theory of mind (ToM) is defined as the ability to detect and reason about other people’s mental states (e.g. their beliefs and intentions), and a deficit in ToM is another reasoning bias that has been linked to psychosis (Brune, 2005). According to this model, deficits in ToM may lead some individuals with psychosis (or at risk for psychosis) to perceive others’ intentions as univocally dangerous or malicious (Frith, 2004). To put this simply, when faced with uncertainty, some individuals will be more likely to assume the worst scenario. Numerous studies have investigated ToM in patients with psychosis and have found clear deficits when compared with non-clinical groups (Ventura et al., 2011).

Deficits in JTC and ToM are likely to work in conjunction with negative schemas (as discussed below) in the development and maintenance of psychotic symptoms. These reasoning biases are activated in the moment-to-moment processing of anomalous experiences and are compounded by particular socio-cognitive factors (e.g. experiences of social adversity, negative schemas of the self and others, low self-esteem) that the individual has been exposed to or formed prior to the anomalous

experiences (Garety et al., 2001; 2007). Experiences of adversity, such as early trauma and continuing negative life events in adulthood, are likely to contribute to an enduring cognitive vulnerability, characterised by negative schematic beliefs about the self and others that serve to facilitate these maladaptive reasoning biases, and unfortunately create an environment in which psychosis can flourish (Garety et al., 2007). These biases are thought to influence the way an individual appraises life events, and can encourage an individual to view the event as having personal significance, being of a threatening nature, and externally caused (Garety et al., 2007). Furthermore, exposure to adult life events that can cause isolation, such as relationship breakdowns and loss of employment, will only serve to increase these reasoning biases, and therefore exacerbate the risk of psychosis.

Negative Schemas

Specific negative beliefs about the self and others have been also proposed to play an important role in the aetiology of psychosis (Fowler, 2000; Garety et al., 2001; Freeman et al., 2002; Fowler et al., 2006b), and have shown associations with psychosis in both clinical (Fowler et al., 2006b; Smith et al., 2006) and non-clinical samples (Freeman et al., 2003). In a now seminal paper, Fowler et al. (2006b) found that in a general population sample of over 700 students, paranoia was associated with negative beliefs about the self and others, less positive beliefs about others, and symptoms of anxiety. Furthermore, the authors also demonstrated that negative schemas were a good predictor of paranoia as they were able to discriminate between the non-clinical sample and a group of patients with psychosis (Fowler et al., 2006b).

Psychologists have proposed that exposure to early adversity (such as childhood trauma) may result in the development of negative beliefs about the self (e.g. as vulnerable, weak and unlovable) and others (e.g. other people are dangerous or untrustworthy). Cognitive models also propose that when an individual experiences subsequent adversity (e.g. negative life events), these schemas about the self and others are likely to become re-activated, which can increase levels of negative affect and influence appraisals of anomalous thoughts and behaviours, potentially giving rise to psychotic experiences (Freeman et al., 1998; Garety et al., 2007). Figure 1.2 shows a simplified model of how experiences of adversity, biased cognitive schema and psychosis may interact.

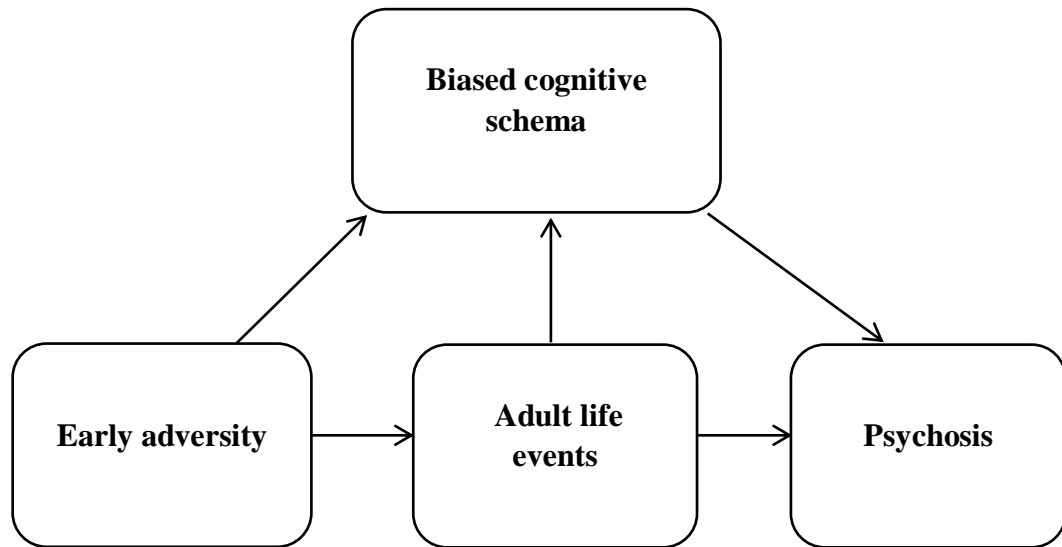


Figure 1.2 A simple model of the potential interrelationships between adversity, negative schemas and psychosis

Affective processes

Research suggests that negative emotional states, including experiences of depression and anxiety, are thought to contribute to the development of positive psychotic symptomatology, such as paranoia, delusional thinking and hallucinations (Freeman, 2007; Bentall et al., 2008; Smith et al., 2006; Freeman & Fowler, 2009). In their cognitive model of persecutory delusions, Freeman et al. (2002) consider persecutory beliefs as an extension of anxious and depressive worries about an individual's own vulnerability and lack of worth, and postulate that these maladaptive emotions are likely to be present prior to the development of psychotic symptoms. Negative affective states may form the beginning of a causal pathway to psychosis as researchers have found that depression and anxiety increase the risk for developing psychotic symptoms, and are strong predictors of transition to disorder (Jones et al., 1994; Krabbendam et al., 2005; Owens et al., 2005). But how are affective symptoms potentially linked to the association between life events and psychosis? Exposure to adverse life events may increase levels of depression and anxiety, which may also form a pathway to later psychotic symptoms. Exposure to adverse life events have been shown to be associated with depression and anxiety (e.g. Ventura et al., 2000; Fowler et al., 2006a), and these symptoms can lead to the later development of psychosis (e.g. Krabbendam et al., 2005; Freeman et al., 2011).

1.6.4. Evidence for specific psychological mechanisms

In terms of the specific psychological mechanisms for life events and psychosis that will be tested in this thesis, i.e. negative schematic beliefs and affective processes, evidence has started to mount but this field is still very much in its infancy. The relevant research to date will be outlined more fully in Chapter 3, and a brief overview is given below.

Since the publication of Garety et al.'s (2007) theoretical paper, research has sought to test the hypotheses of this cognitive model of psychosis and has so far confirmed its predictions. For example, using a general population sample, Gracie et al. (2007) reported that negative beliefs about the self and others partially mediated the relationship between reports of lifetime trauma exposure and paranoid thinking within a student sample. Freeman and Fowler (2009) have reported a role for anxiety in the relationship between lifetime trauma and paranoia in another general population sample. Furthermore, similar cognitive and affective pathways have been found to be involved in the relationship between childhood trauma and psychosis (Fisher et al., 2012). Using a general population sample, Fisher et al. (2012) found that recent anxiety and negative self-beliefs partially accounted for the association between emotional and physical abuse in childhood and later development of paranoia in adulthood. It is clear that research to date which has explored specific psychological pathways from stressful experiences to psychosis is limited by the use of general population samples that may not necessarily be generalisable to individuals experiencing clinical disorder, and therefore further research is needed to see if the theoretical predictions hold true for clinical samples.

1.6.5. Psychological pathways defined for this study

In this study, the specific psychological pathways assessed included negative schemas and affective symptoms. Core schematic beliefs about the self and others (both positive and negative) were measured in all participants using the Brief Core Schema Scale (BCSS; Fowler et al, 2006b). Pre-existing negative beliefs about the self and others were assessed as a potential synergistic factor in the association between life events, difficulties and psychosis.

Levels of depression and anxiety were also measured in all participants using the Hamilton Scales for Anxiety (HAM-A; Hamilton, 1959, 1969) and Depression (HAM-

D; Hamilton, 1960). Total anxiety and depression scores were assessed as a potential mediator in the life events and difficulties-psychosis relationship and a pathway via affective processes was assessed.

1.7. Objectives, Aims and Hypotheses

The main objectives of the work presented in this thesis are to explore associations between adult life events and difficulties and the onset of psychosis in an epidemiologically-derived case-control study, and to explore whether potential psychological pathways of negative schematic beliefs and affective processes are associated with increased odds of psychosis in those exposed to threatening events and difficulties. Cases are individuals with a first presentation of psychosis and controls are individuals with no current or past history of psychotic disorder drawn from the same population as cases.

The aims of this thesis are:

1. To compare the prevalence of adult life events and difficulties in cases and controls;
2. To compare the characteristics of the life events and difficulties reported by cases and controls, e.g. event and difficulty severity, type, intrusiveness, timing, focus, independence, and explore whether these factors are associated with an increased odds of psychosis;
3. To compare schematic beliefs and levels of depression and anxiety in cases and controls, and in controls with PLE;
4. Test theories of a cognitive model of psychosis to examine whether adult life events/difficulties and negative schematic beliefs combine synergistically to increase odds of psychosis, and whether the relationship between adult life events, difficulties and psychosis mediated by affective disturbances (i.e. depressive and anxiety symptoms);
5. Investigate whether the potential pathways between life events, cognitive/psychological disturbances and psychosis are also found within control participants who report sub-clinical psychotic experiences.

In relation to the above aims, four sets of hypotheses were tested, as follows:

Main effects of life events and difficulties on psychosis:

- 1.1. Recent life events and difficulties will be associated with increased odds of psychosis, independent of *a priori* confounders of age, gender, ethnicity, and social class;
- 1.2. The odds of psychotic disorder will be highest in those who have experienced more severe, more frequent, and more intrusive life events and difficulties;
- 1.3. The odds of psychotic-like experiences will be highest in those who have experienced more severe life events and difficulties;
- 1.4. Associations between severe and intrusive life events, difficulties and psychosis will be modified by gender and age, such that stronger effects will be found for women and younger participants;
- 1.5. Independent life events and difficulties will be associated with an increased odds of psychosis;
- 1.6. The odds of psychosis will be higher in those who have experienced severe events and difficulties which are solely subject focused, compared with exposure to joint and other focused events and difficulties;
- 1.7. The odds of psychosis will be higher in those who have experienced severe life events closest to onset (less than 3 months prior to onset), compared with events occurring at other time points (3-6 months, 6-9 months and 9-12 months prior to the onset of psychosis).

Schemas:

- 2.1. Cases will report higher levels of negative schematic beliefs about the self and about others compared with controls;
- 2.2. Controls with PLE will report higher levels of negative schematic beliefs about the self and about others compared with controls without PLE;

Social and Psychological Synergistic Effects:

- 3.1. Severe life events and difficulties will combine synergistically with lower social class status to increase the odds of psychotic disorder beyond the effects of each alone;

3.2. Life events and difficulties will combine synergistically with a) negative schematic beliefs about the self and b) negative schematic beliefs about others, to increase odds of both psychotic disorder and PLE, beyond the effects of each alone.

Affective Symptoms and Mediation:

- 4.1. Cases will report greater levels of anxiety and depression compared with controls;
- 4.2. Controls with PLE will report greater levels of anxiety and depression compared with controls without PLE;
- 4.3. The association between recent life events, difficulties and psychosis (both clinical disorder and psychotic experiences in the control sample) will be mediated by a) higher levels of depression and b) higher levels of anxiety.

1.8. Thesis Outline

This thesis comprises of eight chapters in total (including Chapter 1-Introduction). A brief description of the composition of the remaining seven chapters is briefly outlined below:

Chapter 2 provides an overview and methodological critique of relevant research conducted to date into the association between adult life events, psychotic disorder and psychotic experiences within general population samples, through the use of a systematic literature review and meta-analysis.

Chapter 3 presents the findings from a literature review of specific psychological pathways that may explain associations between adult life events and psychosis onset. It includes a description of the current evidence which argues for a direct link between life events and psychosis (Section 3.1), a discussion of indirect pathways indicated by cognitive models of psychotic symptoms (Section 3.2), and a description of research that has been carried out to investigate the modifying and mediating effects of negative core schemas and negative affect in those reporting exposure to early or recent adversity (Sections 3.3 and 3.4).

Chapter 4 outlines the general methodology of the Childhood Adversity and Psychosis (CAPsy) study from which the data for this thesis are drawn (Section 4.2). This includes detailed descriptions of the LEDS (Brown & Harris, 1989a), which was used to assess adult life events and difficulties in this study (Section 4.4), and also the

Brief Core Schema Scale (BCSS; Fowler et al, 2006b), and Hamilton Scales for Anxiety (HAM-A; Hamilton, 1959; 1969) and Depression (HAM-D; Hamilton, 1960), used to measure the potential psychological mechanisms of core schematic beliefs and affective symptoms (Section 4.5).

Chapter 5 describes the socio-demographic characteristics of the sample used in the study, with reference to those with complete and incomplete data.

Chapter 6 presents the findings of the hypothesis driven main effects analyses of adult life events and difficulties (Hypotheses 1.1-1.7), and also some further exploratory analyses. The first hypothesis driven section presents findings of the associations between various characteristics of the life events data, and occurrence of psychotic disorder and psychotic-like experiences (PLE) within controls (Section 6.3). The second exploratory section presents findings of the investigation between intrusive experiences and PLE, the impact of difficulty duration, and the impact of severe events and difficulties on general symptom severity (Section 6.4).

Chapter 7 presents the results of the associations between schemas and psychotic disorder and PLE (Section 7.4), the synergistic effects of low social class (Section 7.5) and negative schemas (Section 7.6), the association between affective symptoms and psychotic disorder and PLE (Section 7.7), and the mediation analyses of affective symptoms (Section 7.8), (Hypotheses 2.1-4.3).

Chapter 8 summarises and synthesises the findings presented in the preceding chapters, together with a discussion of the methodological limitations of the study, as well as the clinical implications of the findings, and directions for future research.

1.9. Distinct and Original Contributions

This study formed part of a larger ongoing study, the Childhood Adversity and Psychosis (CAPsy) study. Within the larger project I was involved in identifying, consenting and/or assessing approximately 280 eligible participants. My specific contribution involved the weekly screening for new first-episode cases within inpatient and outpatient mental health services, approaching and seeking to consent cases who met inclusion criteria and conducting the full battery of measures and assessments. In preparing the data for analysis for this thesis, I was involved in checking the integrity of the data, through extensive checks of all of the LEDS ratings from 554 participant

interviews of life events and difficulties. I also contributed to the data entry for the overall study, as well as to extensive database cleaning by thoroughly checking for any errors and inconsistencies. I developed the novel aims and hypotheses for this study, and conducted all analyses presented in this thesis.

The work within this thesis which is original is summarised as follows:

- Exploration of the prevalence and impact of recent life events and difficulties in an epidemiologically-derived sample of first-presentation psychosis patients compared to an unaffected control group. This robust study design has yet to be used to investigate this association.
- The use of a gold-standard measure, the LEDS (Brown & Harris, 1989a), to assess the role of recent life events and difficulties, which has never been used in a case-control study of this size. The largest first-episode only sample to use the LEDS had a case sample of 50 participants (Raune et al., 2009), so the sample in this thesis goes far beyond that with a total case sample of 253 participants and an unaffected control sample of 301 participants. Furthermore, this comprehensive measure has not been used to assess the impact of recent experiences on psychotic-like experiences within the general population, where checklist measures tend to be the norm.
- An exploration of the characteristics of the events and difficulties experienced, e.g. their type, severity, intrusiveness. To date, no case-control studies have considered the impact of the type and intrusiveness of recent experiences prior to onset, as measured using the LEDS, and only two first-episode studies have considered the effect of event severity (Faravelli et al., 2007; Raune et al., 2009). However, due to the small case sample in both of these studies, only very tentative conclusions could be drawn, and a comparison of event severity in first-episode cases and population-based controls is still required.
- Assessment of the association between chronic difficulties (lasting between one and twelve months) and the onset of psychosis. To date, there have been no studies which have considered the impact of threatening difficulties on the aetiology of psychosis.

- Investigation of the impact of recent threatening events and difficulties on general psychopathology symptom severity in cases. This has yet to be explored within the existing literature.
- An exploration of the impact of other risk factors on the life events-psychosis association. So far, no clinical study has measured and adjusted for other factors over and above basic demographics. This study will explore the impact of current cannabis use and family history of psychosis (as well as *a priori* confounders of age, gender, ethnicity, and subject's social class).
- Investigation of the potential synergistic effects between low social class and threatening events/difficulties in discriminating between cases and controls.
- Investigation of the synergistic effects between negative core schemas and threatening events in discriminating between cases with psychosis, controls with PLE and controls without PLE. Studies to date have only considered this factor as a potential mediator of the relationship between traumatic experiences and later subclinical psychotic experiences within general population samples (Gracie et al., 2007; Fisher et al., 2012; Freeman et al., 2013).
- Investigation of potential pathways from threatening life events and difficulties, to psychosis onset/subclinical symptoms via anxiety and depression. In previous studies, the pathway between adversity and psychosis via affect has mainly been tested in general population samples (Fisher et al., 2012; Freeman & Fowler, 2009). Furthermore, in those studies that have considered clinical disorder, only pathways from early adversity to psychosis have been considered (Bebbington et al., 2011; Fisher et al., 2013a). Therefore, a pathway from later adverse experiences to clinical disorder, via affective processes, has yet to be explored.

CHAPTER 2 - Adult Life Events and the Onset of Psychosis

Synopsis

It is important that we study the association between proximal adversity and the onset of psychosis in order to advance our understanding of aetiology and improve interventions which target distressing symptoms and seek to decrease relapse. With these ideas in mind, this chapter will open by expanding on a discussion of why it is important to study events prior to onset. The chapter will then progress by examining the nature and strength of the relationship between events and psychosis by systematically reviewing the studies of life events that precede onset. The systematic review and meta-analysis, which forms the bulk of this chapter, was carried out to inform the development of this thesis and includes studies that explored the impact of adult life events prior to the onset of psychotic disorder or the development of subclinical psychotic experiences within general population samples. Studies that failed key methodological requirements, i.e. due to their assessment of events after the onset of symptoms; or where events came before a relapse of psychosis only, or where the dating of events and psychosis could not be determined, were not included in the review and will not be discussed.

The review “Life events and psychosis- a literature review and meta-analysis” was published in *Schizophrenia Bulletin* in May 2013 (Beards et al., 2013). The review includes studies published prior to February 2012 and so an additional section will follow the inserted paper which aims to provide a brief overview of research published and found since this date (until September 2014). This chapter will continue by expanding upon some of the conceptual and methodological issues introduced in the paper, as journal word limit constraints did not permit a detailed discussion. The final section of this chapter will focus on highlighting the gaps in the literature to date and describe how the present study will attempt to address some of these unanswered questions.

2.1. Why investigate the impact of events prior to a first episode of psychosis?

2.1.1. Therapeutic Advancement

If research suggests that life events play some role in the aetiology of psychosis, then a better understanding of this relationship could uncover further (and more refined) targets for prevention and early intervention. If it can be reliably and robustly shown that life events play a role in the onset of psychosis, then preventative interventions could be targeted at a biological, psychological, or social level for individuals within the general public and those at high-risk of disorder who have been exposed to threatening life events. An improved understanding of the role of life events in psychosis should also address the potential pathways and other mediating variables that link the exposure to life events to psychosis onset, and this knowledge could lead to more effective psychological strategies that enhance stress management and coping.

Several early, but key studies, have shown that structured psychosocial interventions, such as family psychoeducation and social skills training (which may reduce environmental stressors), can significantly improve outcome for patients with psychosis, beyond that attained by medical treatments alone (e.g. Leff et al., 1982; Hogarty et al., 1986), and more recent trials suggest some merit for the role of befriending in aiding recovery and improving social functioning (Jackson et al., 2008). Furthermore, Freeman, Garety, and colleagues (Garety et al., 2001; Freeman et al., 2002), suggest that cognitive behavioural therapy (CBT) and family intervention could be helpful in those patients with psychosis who have experienced social adversity. Some of these techniques could also be adopted by services for people at-risk for psychosis, with promising results already reported for the benefits of CBT in reducing progression to psychosis within an at-risk sample (Morrison et al., 2004; Cannon et al., 2008). These psychosocial techniques may enable an at-risk sample to minimise their exposure to threatening events that are within their control and therefore potentially preventable, but also these interventions may increase their ability to cope if an event occurs, which could ultimately prevent new cases of psychosis from emerging.

An appreciation of the impact of life events on psychosis onset could also be an important discussion point in therapy sessions for those who have already developed their first episode of psychosis. Fowler (2000) supports the idea of assisting individuals with a first episode of psychosis to gain a wider understanding of how their personal history and symptomatology interact with each other, and this increased awareness is

likely to be beneficial to recovery. Furthermore, it may be helpful for all health care professionals to be more mindful of the impact of life events on mental health and to be available to provide more proactive support after exposure to a threatening event.

The experience of stressful events is likely to influence not just the onset of symptoms, but may also affect the outcome of psychosis in a variety of different ways. For instance, exposure to certain events may influence the course of illness that subsequently develops, with research suggesting that where onset is driven by stress, these individuals may be less likely to develop a severe illness progression (Castine et al., 1998), and are less likely to relapse (van Os et al., 1994). In an extensive follow-up study of the Camberwell Collaborative Psychosis Study, van Os et al. (1994), found that individuals with schizophrenia who reported a stressful life event in the three-month period prior to onset had milder symptom severity, reduced amount of time in hospital and were given less medication than patients who did not report any events prior to onset. These findings have important implications for therapeutic practice and suggest that individuals who present with a first episode of psychosis without an apparent environmental trigger may be at increased risk for a worse illness course.

The experience of recent life events might be particularly relevant in earlier episodes, as recurrent episodes (more than three episodes) appear less related to the experience of life events (Castine et al., 1998). Patients with a long-standing disorder may become more sensitised as their illness progresses and so relapse may be less associated with stress. It may therefore be the association of severe events with psychosis is strongest in relation to onset; an effect which has been demonstrated for patients with depression (Brilman & Ormel, 2001) and bipolar disorder (Ghaziuddin et al, 1990; Post, 1992). However, with the current lack of robust literature which assesses the role of life events in psychosis onset, the suggestions that life events may be important for initial episodes of psychosis must be treated cautiously.

A history of stress and trauma may also influence response to medication and could contribute to treatment resistance. In their cognitive model of positive psychotic symptoms, Garety et al. (2001) propose that experiences of early trauma and chronic stress can lead to the development of dysfunctional negative schemas, which can impact on patient's thoughts and behaviours concerning medication and therapeutic engagement; therefore increasing their vulnerability to relapse. This proposition is supported by studies showing that exposure to stressful events may interact differently with risk of psychosis, depending on whether patients are receiving antipsychotic medication (e.g.

Leff et al., 1973; McEvoy et al., 1984; Ventura et al., 1992). Interestingly, Leff et al. (1973) found that patients receiving a medication regime experienced more life events in the five-week period before relapse, than patients who relapsed whilst receiving a placebo drug (89% versus 31%). These findings suggest that antipsychotic medication can provide some protection against relapse, but it may not be sufficient to withstand the additional impact of adverse life events beyond a certain threshold. The authors proposed that a relapse whilst on medication is unlikely unless a major life event occurs, and this can partially explain why relapses are more highly associated with life events in patients on medication than in non-medicated patients. However, no firm conclusions can be made regarding the links between events and medication status as other studies have not found any evidence of associations between medication, life events and risk of relapse (Hirsch et al., 1996), and this continues to be a contested area of research (Phillips et al., 2007).

2.1.2. Theoretical Reasons

The stress-vulnerability model of psychosis, developed by Zubin and Spring (1977), suggests that the experience of stress is essential to the onset of acute psychosis; however this model and many others were developed with limited support from methodologically robust first-episode studies. In an early review of life events and mental illness, Dohrenwend and Dohrenwend (1978) concluded that the idea that life stress can cause illness is supported more by faith (or perhaps, common sense!) than scientific evidence. Comprehensive models of relapse have subsequently been proposed (e.g. Nuechterlein et al., 1994), which have stronger evidence-based support (e.g. Leff et al., 1983; Ventura et al., 1989; Malla et al., 1990) to support the role of life events in psychotic relapse, but there is clearly a dearth of research to support models of aetiology. If events can be shown to precede the first episode of psychosis in methodologically robust studies, then the proposal of their hypothesised role in both onset and relapse will be better supported.

There are also some advantages to using a first-episode design. Yung (1998) has highlighted that there is a reduction in potential confounders, including chronic illness, institutionalisation, and complex co-morbidities, including comorbid substance use (Kavanagh et al., 2004). A further consideration for non-first-episode research is the impact of probable deteriorations in memory and cognitive functioning, which are commonly seen in patients with a chronic illness (Heinrichs & Zakzanis, 1998). Overall,

the study of first episode samples allows questions to be considered which are unique to onset and also minimises the impact of variables which might confound any aetiological interpretation. However, studying the first episode does not automatically overcome all methodological weaknesses, as will be discussed within the paper and the expanded discussion which follows.

[**Start of paper:** Beards S, Gayer-Anderson C, Borges S, Dewey ME, Fisher HL, Morgan C (2013). Life events and psychosis: a review and meta-analysis. *Schizophrenia Bulletin*, 39 (4): 740-747]

2.2. Life Events and Psychosis: A Literature Review and Meta-Analysis

Recent models of psychosis implicate social adversity, broadly defined, in its aetiology (Garety et al., 2001; Selten & Cantor-Graae, 2005). However, while evidence has accumulated for childhood trauma (Morgan & Fisher, 2007; Varese et al., 2012), the role of adult life events has received less attention. Life events are situations or occurrences that bring about a positive or negative change in personal circumstances and/or involve an element of threat. As a basis for further research, it is important to evaluate existing research on life events and psychosis, both in terms of substantive findings and methodological issues. This review focuses on the impact of adult life events on risk of both onset of psychotic disorder and subclinical psychotic experiences in general population samples.

A recent review by Fallon (2008) evaluated studies that used semi-structured interview measures to assess exposure to life events in psychosis patients. Because the literature in this area is still fairly small, a more extensive, systematic, and updated review of the literature was considered to be the most appropriate strategy to better understand the association between adult life events and psychosis. Given previous concerns about the methodological quality of studies of life events and psychosis (Fallon, 2008), a quality assessment tool was devised to evaluate the selected studies. This review focuses on the most robust studies.

2.2.1. Method

A systematic search of relevant databases was conducted using predefined search terms. The following search terms were applied to PsychINFO, Medline, EMBASE and Web of Science: adult advers* OR social advers* OR life event* OR lifetime trauma OR traumatic event. Using the Boolean operator 'AND', these were combined with psychosis-related search terms: psychosis OR psychoti* OR schizo* OR hallucinat* OR voice* OR delusion* OR paranoi* OR thought disorder. Studies were included if: a) they assessed life events in adulthood; b) the individuals were over 16 years; c) the individuals had a first episode of psychosis or subclinical psychotic experiences; and d) they were published in English in peer reviewed journals. Studies were excluded if: a) they assessed childhood events only; and b) no distinction was made between childhood and adulthood in timing of exposure. Adulthood was defined as aged 17 years. Each study was assessed using a quality assessment tool (see Appendix A). A cut-off score of at least 10 out of 14 (over 70%) was chosen to select the more 'methodologically robust' studies. Although this may be arbitrary and risks leaving out any study that scores high on some and low on other criteria, it does ensure consideration of only the most consistently robust studies.

2.2.2. Results

Sixteen studies published between 1968 and 2012 met the inclusion criteria (see Figure 2.1), a surprisingly small number. Eleven were studies of clinical samples (six of first-episode cases and five of mixed first and non-first-episode cases) and five of general population samples (see Table 2.1, 2.2 and 2.3). Fourteen studies reported a positive association between adult life events and onset of psychotic disorder or occurrence of subclinical experiences. Within the clinical studies, cases with psychosis were over two times (Raune et al., 2009) to eight times (Canton & Fraccon, 1985) more likely to report life events compared with controls in the period leading up to onset. In the general population studies, those with psychotic experiences (vs. those without) were between two times (Johns et al., 2004) and seven times (Jenkins et al., 2010) more likely to report recent life events.

The picture is the same when only those studies (Brown & Birley, 1968; Dohrenwend et al., 1987a; Gureje & Adewunmi, 1988; Bebbington et al., 1993; Faravelli et al., 2007; Raune et al., 2009; Lataster et al., 2012) that received a quality

score of 10 or above ($n=7$) are considered, i.e. six studies (Brown & Birley, 1968; Dohrenwend et al., 1987a; Bebbington et al., 1993; Faravelli et al., 2007; Raune et al., 2009; Lataster et al., 2012) reported some evidence that the number and/or severity of events was associated with around a three to five-fold increased risk of psychosis.

Timing

The majority of these more robust studies found life events were elevated prior to onset of psychosis, with the time period under consideration ranging between three months (Brown & Birley, 1968) and three and a half years (Lataster et al., 2012). The seminal article of Brown and Birley (1968), for example, found life events were increased in the three-week period pre-onset of psychotic symptoms. The sample, however, was small ($n=50$, 13 of whom were non-first-episode) and no subsequent studies have reported similar findings. Later studies suggest that life events may exert their influence over a longer period. For example, two studies (Dohrenwend et al., 1987a; Faravelli et al., 2007) of disorder found life events were around two to three times higher in cases compared with controls across a one year period. Further, a general population study (Lataster et al., 2012) of 1722 young adults found that exposure to life events over the previous three years was associated with an increased risk of psychotic experiences.

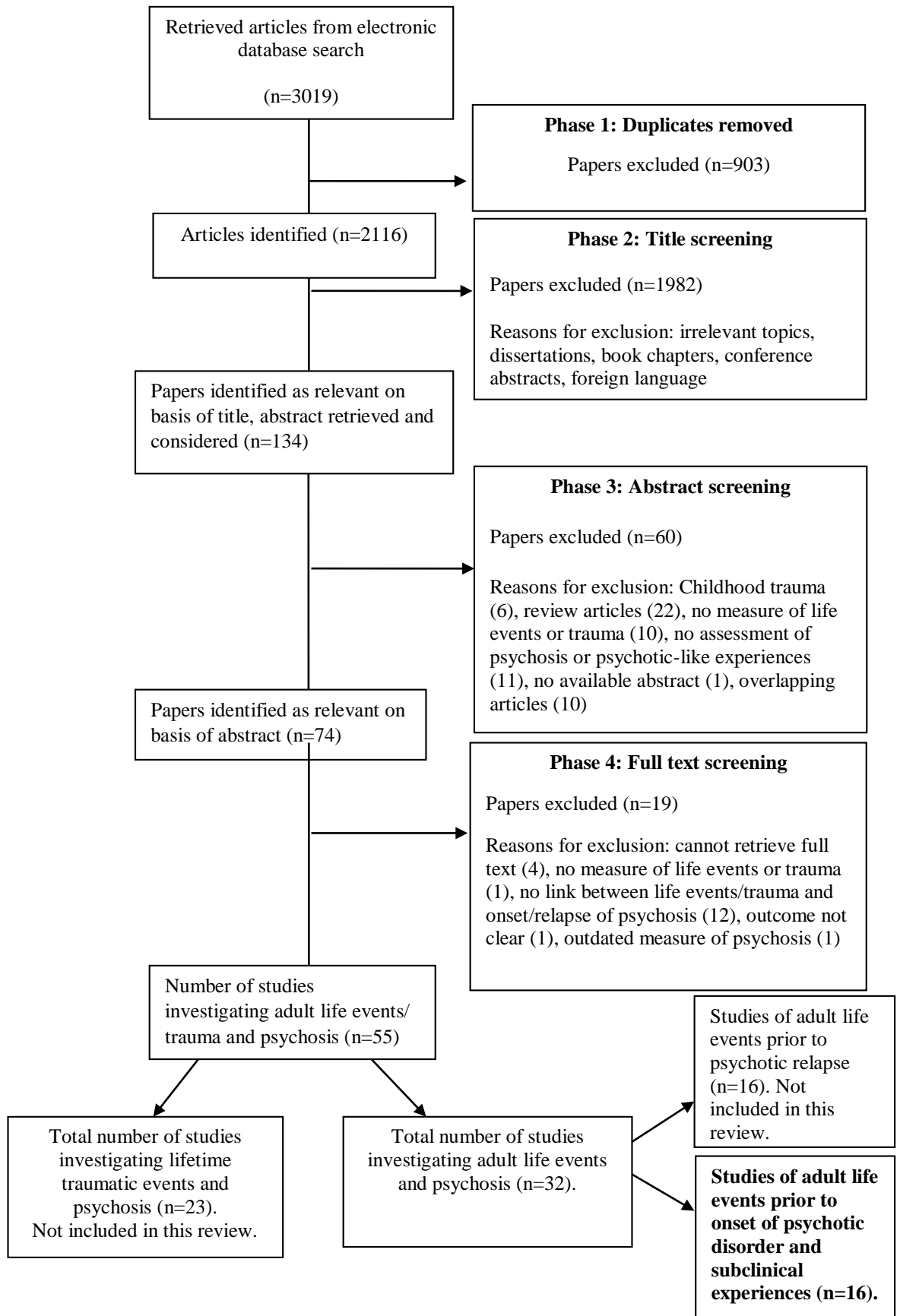


Figure 2.1 Flow chart for paper selection

Table 2.1 Studies Investigating the Associations Between Adult Life Events and Psychosis in First-Episode Samples

Authors, Location	Design	Sample	Measure of Life Events	Life Events Period	Measure of Psychosis	Main Findings	Quality Score
Day et al. (1987), WHO international study	Within-patient	386 cases with psychosis	WHO Life Events Schedule (WHO LES, 1978, unpublished)	3 months prior to onset of psychosis	ICD-9 diagnoses (including PSE and CATEGO, where possible)	Number of patients reporting life events 3 months prior to onset ranged from 21% - 87%	9
Gureje & Adewunmi (1988), Nigeria	Case-control	42 cases with psychosis and 50 population controls	Paykel's life events checklist (Paykel et al., 1969)	6 months prior to onset (cases) or interview (controls)	Research Diagnostic Criteria (Spitzer et al., 1975) for schizophrenia	Life event 1 month prior to onset/interview: cases: 7%, controls: 24% ($\chi^2= 8.26$, $p<0.01$)	10
Chakraborty et al. (2007), India	Between-patient	18 cases with acute and transient psychotic disorder and 20 control patients with mania	Presumptive Stressful Life Events Scale (Singh et al., 1984)	Lifetime and within 6 months prior to onset (cases) or interview (manic patients)	Consensus decision and ICD-10 criteria	Mean number of negative life events 2 weeks prior to onset/interview: cases: 0.72 (SD 0.95), manic patients: 0.20 (SD (0.52), ($U= 110.0$, $p=0.013$)	7
Faravelli et al. (2007), Italy	Case-control	9 cases with psychosis and 123 population controls	LEDS (Brown & Harris, 1989a)	1 year prior to onset (cases) or interview (controls)	Florence Psychiatric Interview (Faravelli et al., 2001), which produced DSM-IV diagnoses	Severe life events 1 year prior to onset/interview: cases: 9 (33%), controls: 123 (12%), (OR 3.2, 95% CI 0.7-15.5, not significant)	10

Authors, Location	Design	Sample	Measure of Life Events	Life Events Period	Measure of Psychosis	Main Findings	Quality Score
Raune et al. (2009), United Kingdom	Within-patient cluster design (with case-control comparisons)	41 cases with psychosis and 548 population controls	LEDS	1 year prior to onset (cases) or interview (controls)	ICD-10 diagnosis of psychosis (from SCAN)	Moderate to severe independent life event 3 months prior to onset: cases: 14 (34.1%), controls: 42 (13.5%), (OR= 5.0, 95% CI 2.4-10.7)	11
Mondelli et al. (2010), United Kingdom	Case-control	50 cases with psychosis and 36 population controls	List of Threatening Experiences (Brugha & Cragg, 1990)	6 months prior to onset (cases) or interview (controls)	ICD-10 and DSM-IV criteria for psychosis using the Operational Criteria (OPCRIT) (McGuffin et al., 1991)	Number of life events in previous 6 months: cases: 2.3 (SD 0.3), controls: 0.7 (SD 0.2), ($t=-4.8$, df (1, 81), $p<0.001$)	5

Note: CATEGO, Categorical assessment of psychiatric disorder; ICD, International Classification of Diseases; PSE, Present State Examination; LEDS, Life Events and Difficulties Schedule; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; SCAN, Schedules for Clinical Assessment in Neuropsychiatry.

Table 2.2 Studies Investigating the Associations Between Adult Life Events and Psychosis in Mixed Onset and Relapse Sample

Authors, Location	Design	Sample	Measure of Life Events	Life Events Period	Measure of Psychosis	Main Findings	Quality Score
Brown & Birley (1968), United Kingdom	Case-control	50 cases with psychosis and 325 population controls	Early version of the Life Events and Difficulties Schedule (LEDS)	13 weeks before onset (cases) or interview (controls)	Present State Examination (PSE; Wing et al., 1967)	Independent life event in 3 weeks pre-onset or interview: cases: 46%, controls: 14%, (p<0.001)	11
Canton & Fraccon (1985), Italy	Case-control	54 cases with schizophrenia, recent onset (n=24), chronic (n=30), and 54 control subjects	Paykel's Interview for Recent Life Events (Paykel & Mangen, 1980)	6 months preceding hospital admission (cases) or interview (controls)	DSM-III diagnosis of schizophrenia	Exposure to more than two life events 6 months prior to psychosis/interview: cases: 33 (61%), controls: 4 (7%), (p<0.001)	9
Al Khani et al. (1986), Saudi Arabia	Case-control	48 cases with schizophrenia, first episode (n=21), previous episodes (n=27), and 62 population controls	WHO Life Events Schedule	1 year prior to onset/relapse (cases) and interview (controls)	Arabic version of PSE and CATEGO	Life event in 6 months prior to psychotic episode/interview: cases: 88%, controls: 71%, (not significant; precise p not reported)	9
Dohrenwend et al. (1987a), United States	Case-control	66 cases with schizophrenic disorder (21 first-onset) and 197 population controls	Psychiatric Epidemiology Research Interview (PERI; Dohrenwend et al., 1978)	1 year prior to onset/relapse (cases) and interview (controls)	DSM-III diagnoses	Mean number of 'non-fateful' life event in 1 year prior to psychotic episode/interview: cases: 0.89, controls: 0.25, (p<0.001)	12

Authors, Location	Design	Sample	Measure of Life Events	Life Events Period	Measure of Psychosis	Main Findings	Quality Score
Bebbington et al. (1993), United Kingdom	Case- control	97 cases with psychosis and 207 population controls	LEDS	6 months prior to onset (cases) or interview (controls)	DSM-III diagnoses	Severe life events 3 months prior to onset/interview: cases: 27 (52%), controls: 21 (10%), ($\chi^2=$ 69.05, $p<0.001$)	12

Table 2.3 Studies Investigating the Associations Between Adult Life Events and Psychosis Experiences in General Population Samples

Authors, Location	Design	Sample	Measure of Life Events	Life Events Period	Measure of Psychotic Experiences	Main Findings	Quality Score
Vinokur & Selzer (1975), United States	Cross-sectional	1059 male subjects	Social Readjustment Rating Scale (Holmes & Rahe, 1967)	1 year prior to interview	Paranoid thinking assessed using a self-report questionnaire	Positive correlation between life events and self-reported paranoid thinking ($r=0.33$, $p<0.01$)	2
Johns et al. (2004), United Kingdom	Cross-sectional	Random sample of 8520 adults. 478 (5.5%) reported >1 psychotic symptoms in the past year	List of Threatening Experiences (LTE)	6 months prior to interview	Psychosis Screening Questionnaire (PSQ; Bebbington & Nayani, 1995)	Life event in past 6 months: yes: 2136 (25%), no: 6384 (75%), (OR 2.20, 95% CI 1.82-2.66, $p<0.001$)	9
Jenkins et al. (2010), Tanzania	Cross-sectional	Random sample of 899 adults. 35 (3.9%) reported >1 psychotic symptoms in the past year	Life events checklist, based on the LTE (Jenkins et al., 1997a/b)	6 months prior to interview	PSQ	2 or more life events in past 6 months: yes: 117 (13%), no: 782 (87%), (OR 7.45 95% CI 3.42-16.21, $p<0.001$)	9
van Nierop et al. (2012), the Netherlands	Cross-sectional	Random sample of 6646 adults. 1078 (16%) endorsed >1 lifetime psychotic experience	LTE	1 year prior to interview	Composite International Diagnostic Interview (CIDI; Kessler & Ustun, 2004)	Negative life events in past year: psychotic experiences group: 249 (66%), controls: 2541 (48%), (RR 2.07, 95% CIs 1.66-2.57, $p<0.001$)	7

Authors, Location	Design	Sample	Measure of Life Events	Life Events Period	Measure of Psychotic Experiences	Main Findings	Quality Score
Lataster et al. (2012), the Netherlands	Cross- sectional	Random sample of 1722 young adults. 170 (9.9%) endorsed >1 lifetime psychotic experience	Munich Interview for the Assessment of Life Events and Conditions (MEL; Maier-Diewald et al., 1983)	An average of 3.6 years prior to interview	CIDI	Mean number of negative life events: psychotic experiences group: 7.49, controls: 5.98, ($t=-4.17$, df, (1, 1720), $p<0.001$)	12

Note: RR, relative risk.

Severity and Type

Some studies assessed other contextual elements of events, such as their severity and type. In a study of 97 cases (35 first-episode) and 207 controls, Bebbington et al. (1993), found that moderate and severe life events (vs. mild) were higher in the three-month period pre-onset in patients with schizophrenia (i.e., 52% cases with moderate/severe events vs. 10% controls).

More specifically, using a sample of 41 first-onset patients, Raune et al. (2009), found that intrusive events, such as a physical assault or invasive operation, were more likely to be associated with an increased risk of psychosis and were most common in the three months pre-onset (i.e., 34% cases vs. 3% controls). However, for these analyses the control sample was taken from two studies (Bebbington et al., 1981; Harris, 1987), conducted 20 years previously.

Others have found evidence for specific effects for certain types of events. Dohrenwend et al. (1987a), for example, in a sample of 66 schizophrenia cases (21 first-onset) and 197 population-based controls, found physical illness and injury (akin to intrusive events) were around two times more common in cases than controls.

Independence of events

One way of clarifying the causal relationship between events and onset is to distinguish events that are independent of emerging symptoms, e.g. death of a close relative, from those which may be influenced by mental state e.g. inter-personal conflict.

Five of the more robust studies (Brown & Birley, 1968; Dohrenwend et al., 1987a; Bebbington et al., 1993; Faravelli et al., 2007; Raune et al., 2009) distinguished between possibly dependent and independent events. For example, Brown and Birley (1968) found 46% of cases were exposed to recent independent events compared with 14% of controls. More recent research suggests similar conclusions (Bebbington et al., 1993; Faravelli et al., 2007; Raune et al., 2009). Raune et al. (2009), for example, found that almost all cases (95%) experienced a life event one year prior to the development of symptoms and that in 76% these event(s) were independent. These authors also found that cases were two times more likely to report independent life events in the three months pre-onset than controls (34% cases versus 14% controls).

In contrast, Dohrenwend et al. (1987a), did not find any increase in independent events prior to onset. However, they did find a higher number of ‘non-fateful’ events (a similar concept to dependent events, i.e. events which are influenced by prior mental

state and personality characteristics, such as relationship difficulties) in the year prior to onset.

2.2.3. Meta-Analysis

Additionally, we carried out a meta-analysis of a subset of thirteen studies in which the number exposed and not exposed to life events had been reported (Brown & Birley, 1968; Canton & Fraccon, 1985; Al Khani et al., 1986; Dohrenwend et al., 1987a; Gureje & Adewunmi, 1988; Bebbington et al., 1993; Johns et al., 2004; Faravelli et al., 2007; Raune et al., 2009; Jenkins et al., 2010; Mondelli et al., 2010; Lataster et al., 2012; van Nierop et al., 2012) (see Appendix B for more detail on the methods for the meta-analysis).

The meta-analysis yielded an overall weighted OR of 3.19 (95% CI 2.15-4.75), which suggests that individuals with psychotic disorder/experiences are roughly three times more likely than controls to be exposed to recent life events (Figure 2.2). The OR from the clinical samples (Brown & Birley, 1968; Canton & Fraccon, 1985; Al Khani et al., 1986; Dohrenwend et al., 1987a; Gureje & Adewunmi, 1988; Bebbington et al., 1993; Faravelli et al., 2007; Raune et al., 2009; Mondelli et al., 2010) are higher than the general population studies (Johns et al., 2004; Jenkins et al., 2010; Lataster et al., 2012; van Nierop et al., 2012), but this was not statistically significant. There is substantial heterogeneity between studies (Higgins' $I^2=87.27\%$ (95% CI 70.34%-96.36%). The heterogeneity was not removed by meta-regression using any of the four possible moderators (year of publication, life events period, quality score and type of sample, i.e., clinical or general population), possibly due to rather restricted variability on all of them.

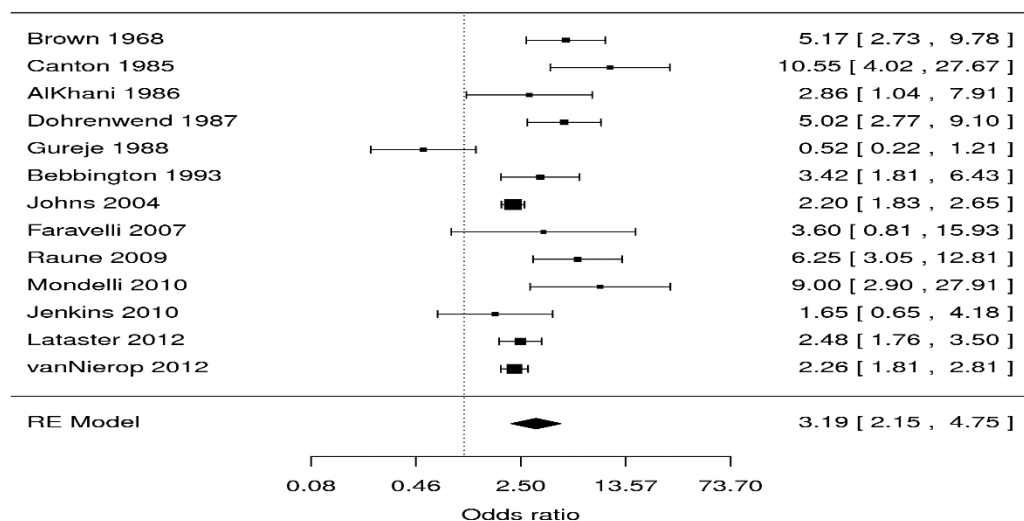


Figure 2.2 Forest plot for the meta-analysis examining the overall association between recent life events and psychosis

2.2.4. Methodological Issues

Across all studies, there were a number of common methodological issues that merit specific consideration. Firstly, the majority of studies were cross-sectional, introducing potential recall bias and limiting inferences concerning direction of causation. In relation to psychotic disorder, it is difficult to envisage longitudinal studies being feasible, given the low incidence of disorders. Consequently, efforts to minimise recall bias and carefully date exposure to events and onset of disorder are essential, but were rarely made.

Further, not all the studies in this review included a comparison group, and, of the ten that did Brown & Birley, 1968; Canton & Fraccon, 1985; Al Khani et al., 1986; Dohrenwend et al., 1987a; Gureje & Adewunmi, 1988; Bebbington et al., 1993; Chakraborty et al., 2007; Faravelli et al., 2007; Raune et al., 2009; Mondelli et al., 2010), not all drew controls from the same populations as cases. Bias in selection of comparison group(s), therefore, cannot be excluded.

Within the clinical studies, causal interpretations are limited by the small number of first-episode only samples and by the failure of papers based on mixed samples to report findings specifically for first-episode cases. This noted, both types of

study in the main reported positive associations. It is clear that more first-episode studies are needed, which utilise appropriate control groups and objective ratings of the impact of events.

Differences in life events measurement make comparisons between studies difficult and this may account for some of the variations in findings. Instruments to assess life events generally fall into two categories: checklist or semi-structured interview. The Life Events and Difficulties Schedule (LEDS; Brown & Harris, 1989a) is considered the gold standard as it takes account of context, e.g. timing, severity and independence of events. It is, however, time consuming to administer and rate. Of the studies reviewed, four used checklists (Vinokur & Selzer, 1975; Johns et al., 2004; Jenkins et al., 2010; van Nierop et al., 2012); two used a checklist that was interviewer administered (Gureje & Adewunmi, 1988, Mondelli et al., 2010); ten used semi-structured interviews (Brown & Birley, 1968; Canton & Fraccon, 1985; Al Khani et al., 1986; Day et al., 1987; Dohrenwend et al., 1987a; Bebbington et al., 1993; Chakraborty et al., 2007; Faravelli et al., 2007; Raune et al., 2009; Lataster et al., 2012), of which four (Brown & Birley, 1968; Bebbington et al., 1993; Faravelli et al., 2007; Raune et al., 2009) used the LEDS (Brown & Harris, 1989a). Of these latter studies, three (Brown & Birley, 1968; Bebbington et al., 1993; Raune et al., 2009) found positive associations between recent life events and psychosis onset.

Where the severity of life events was evaluated, this was mainly determined using objective criteria and not based on subjective appraisals. This is because subjective perceptions of severity may be affected by mood and mental state, which would then risk confusing exposure and outcome and make it impossible to distinguish cause and effect.

While most of the assessments of life events used in the reviewed studies do enquire about positive events, only one of the studies drew a distinction between positive ('desirable') and negative ('undesirable') events in their analyses (Chakraborty et al., 2007), finding associations only for negative events and psychosis. No study specifically discussed the valence of events in relation to psychosis onset.

Finally, adjustment for potential confounders was inconsistent. Where adjustments were made, the majority controlled for age, gender and ethnicity, with some controlling for a wider range of factors, such as urbanicity, education, IQ, substance use,

co-morbid neurosis (Johns et al., 2004); and past year cannabis use (Jenkins et al., 2010). No study adjusted for childhood adversity.

2.2.5. Discussion

There were three main findings: a) the literature on adult life events and psychosis onset is surprisingly small (only 16 studies spread over 44 years); b) most studies suggest the number of events prior to onset is higher (compared with a comparison group) in those with psychosis or psychotic experiences, with our meta-analysis suggesting around a three-fold increased odds of life events in the period prior to psychosis onset; and c) more tentatively, there are some indications that intrusive events may be particularly relevant to the development of psychosis. These findings noted, much of the existing research is methodologically limited and this necessarily urges caution in drawing any inferences about the aetiological role of life events in psychosis.

2.2.6. Life Events and Psychosis

Interest in the role of life events in the onset of psychosis has fluctuated in the time since Brown and Birley's (1968) seminal study. In recent years there has been a resurgence of interest in the role of social factors in psychosis aetiology. Within this context, it is important to revisit the question of whether exposure to proximal stressors (i.e. life events) increases risk of psychosis. The literature is suggestive, but too weak to permit firm conclusions.

The suggestion that life events may increase risk is nonetheless strengthened by the emergence of plausible mechanisms that may account for how exposure to external stressors can impact on individuals in ways that increase risk for psychosis. For example, drawing from cognitive models of psychosis, it is possible that exposure to, say, threatening and intrusive events influence how individuals appraise their social worlds, perhaps leading to hostile perceptions of the external world (Garety et al., 2001). Repeated exposure may contribute to pushing some along a continuum from suspiciousness to paranoia to persecutory delusions. More biologically, there is now evidence of HPA axis dysregulation in psychosis. Stress-induced dysregulation of the HPA-axis may subsequently give rise to increased dopamine receptor densities and dopamine release (Walker & Diforio, 1997), mirroring dopaminergic abnormalities

commonly thought to be present in psychosis. The association between adult life events and psychosis may also be influenced by genetic susceptibility, be it as a result of an underlying variation in DNA sequence or because of epigenetic variation in gene expression.

In sum, there is evidence to suggest adult life events may be relevant to the onset of psychosis for some, and there are plausible mechanisms through which such exposures may work. However, the existing literature is disparate and methodologically weak. To more fully understand the nature of the link, if any, between life events and psychosis, there is a need for a new generation of studies that pay close attention to careful assessment of events, that include robust comparison groups, and that seek to minimise the inherent recall and selection biases. Exposure and responses to life events are potentially modifiable and a better understanding of how they impact on risk of psychosis may inform strategies for prevention and early intervention.

[End of paper]

2.3. Update

Since the review was submitted for publication, four other studies (Wigman et al., 2011; Sharifi et al., 2012; Rusaka & Rancans, 2014; Gallagher et al., 2014) were found and considered relevant for discussion in this chapter. The first two papers report data concerning the impact of recent life events on psychotic experiences using general population samples (Wigman et al., 2011; Sharifi et al., 2012), and the other two assess a first episode sample (Rusaka & Rancans, 2014; Gallagher et al., 2014).

Using a prospective design, Wigman et al. (2011) analysed a Belgian twin sample of 556 women (aged 18-45 years) to see if exposure to stressful life events predicted the expression of subclinical psychotic experiences over a two year time period. Individuals were assessed for the presence of subclinical psychotic symptoms during three sessions over the course of two years, and at the end of the study were divided into two groups: a ‘persistent’ group and a ‘low’ expression group. The ‘persistent’ or subclinical psychosis group displayed a high initial level of positive psychotic experiences and these scores nearly doubled by the end of the study period (unstandardized slope 0.48). This subclinical group consisted of 70 individuals (12% of the total sample). In contrast, the ‘low expression’ group, which contained the rest of

the sample (88%, $n=496$), were characterised as having low levels of initial subclinical psychotic experiences and a small but statistically significant decrease in experiences over time (unstandardized slope 0.06). The researchers found that exposure to trauma, both in childhood ($OR=3.26$) and in recent adulthood ($OR=3.15$) was associated with membership of the subclinical psychosis group, suggesting that the persistence of subclinical psychosis is influenced by exposure to adversity across the lifetime. However, the generalisability of these findings is unclear as the unique sample contains a high proportion of well-educated and high functioning women twins of solely White Belgian ethnicity. It would be interesting to extend this methodology to include men and include a broader range of ethnicities and age groups. Further research could also focus on following up the sample to see whether the experience of stressful life events predicts the transition to psychotic disorder in later life. However, given how rare psychotic disorder is, this may not be a realistic possibility, as the initial sample size would need to be much larger.

The other general population study aimed to examine the correlates of self-reported psychotic symptoms in an urban area of Iran (Sharifi et al., 2012). Using a cross-sectional design, 2158 individuals (aged 18-65 years) in southern Tehran were interviewed to assess the severity of psychotic symptoms over the past month and were asked about the frequency and severity of stressful life events over the previous six months. Moderate positive correlations were observed between stressful life events, both their frequency ($r=0.37$) and stressfulness ($r=0.39$), and self-reported psychoticism; and between the frequency ($r=0.41$) and stressfulness ($r=0.39$) of events and paranoid ideation. According to the final regression model presented, the severity of stressful life events was independently associated with the level of psychoticism, whereas the frequency of events was independently associated with paranoia. One of the key limitations with this study is the self-report measure (SCL-90-R) used to assess psychotic experiences as it relies on individuals being able to correctly interpret complex phenomena. However, the authors did try to address this problem by running a parallel study alongside it. This sub-study tested the psychotic-relevant items from the self-report measure for its validity and utility against DSM-IV diagnoses using a clinical sample of psychotic and nonpsychotic patients. The authors found that the self-report measure chosen was capable of detecting psychotic symptoms in the present study setting, and so appears to be an adequate measure for this large sample.

The first of the two first-episode studies (Rusaka & Rancans, 2014) explored the impact of life events prior to a first episode of acute and transient psychotic disorder (ATPD) in Latvian patients. The recent life histories of 294 consecutively hospitalised patients with their first-episode of illness were assessed using a retrospective chart review approach. The researchers found pre-onset stressful life events to be fairly common with 43.8% (n=129) of patients reporting exposure within six months prior to the diagnosis of the first episode. Some slight gender differences were found with 56.5% (n=73) of men and 43.4% (n=56) of women experiencing recent events. The most common types of events experienced were relating to work and education, and included recent unemployment, change of job or school, and serious problems at work. The use of the chart-review approach, as opposed to using a structured life events scale, seriously weakens this study as it relies on the accuracy of health professionals' written accounts, which has substantial potential for missing information and is prone to many uncontrollable biases. Furthermore, the lack of a control group means that we are unable to know whether stressful life events increases the odds of ATPD compared to unaffected controls in this particular population.

The second of the two first-episode studies (Gallagher et al., 2014) explored the effect of severe stressful life events on the onset of specific symptoms of schizophrenia. The medical records of 431 patients with schizophrenia were assessed and the information was used to rate the nature and severity of psychotic symptoms, parental socioeconomic status (SES) at the time of the patients birth, and the number of life events experienced prior to onset (broken down into social network events, health, military and other). The authors reported an elevated risk for positive psychotic symptoms among low SES patients who had experienced a stressful life event prior to symptom onset ($\chi^2= 5.418$, $p<0.02$), with 81.8% (n=36) of low SES patients experiencing both a pre-onset stressful life event and positive symptoms. Similar effects were not found for high SES patients and the authors concluded that low SES patients have a heightened reactivity to stressors. This study is subject to the same limitations highlighted above, i.e. use of medical records to assess life events (and also symptoms and SES), and no control group. Further limitations include using parental SES at birth as a way of better understanding the relationship between recent adult life events and schizophrenia. Although the mean age of the subjects in this study was for some reason not stated, it is likely that at least a couple of decades have passed since the subjects' birth, and although for many subjects, their current social class level may remain

unchanged from their parents, there may be some who have moved up or down the social hierarchy, possibly as a result of education or work opportunities. Furthermore, previous research suggests that social class differences found between individuals with probable psychosis and unaffected individuals within the general population are unlikely to be driven by parental social class status, and the drift towards lower social class status often starts in adolescence with poor academic and/or employment achievement (Singleton et al., 2001). Further weaknesses within the Gallagher et al. (2014) study include the lack of dating of the life events, and although the researchers specifically searched for adult events occurring pre-onset, it is likely that there will be more errors when using this chart-based approach than using a face-to-face interview.

In conclusion, these four additional studies provide some further data relevant to the question addressed in the systematic review and meta-analysis. Exposure to stressful life events appear to precede, and may contribute to, the onset of psychotic disorder and experiences. There is however, a need to further explore this association with a well-defined first-episode sample and pay much closer attention to the timing and nature of the antecedent events.

2.4. Extended discussion on conceptual and methodological considerations

Some of the variability seen in the studies reviewed above suggest that life events are probably only one of a number of factors that contribute to the development of a psychotic episode. There are also a range of methodological shortcomings associated with this research that might contribute to the different results that have been reported. Some of these issues were briefly highlighted in the paper above, but the next section of this chapter will expand more fully on the considerations and methodological issues which are specific to the study of life events and first episode psychosis.

In an attempt to address the main methodological weaknesses associated with life events studies in schizophrenia, Bebbington and Kuipers (1992) proposed a set of requirements that should be taken into consideration, and these include: a standardised method of symptomatic assessment, standardised method of case definition, limitation to cases where it is possible to date onset accurately, onset defined as a move from an effectively symptom-free period before onset, precise dating of events to identify the salient period of interest, objective rating of the impact of events, objective rating of the degree to which events are independent of actions of the subject that might have been

due to emerging illness, and an appropriate control group. With these important requirements in mind, the following paragraphs will further expand upon some of these issues that are relevant to linking life events with first episode psychosis.

2.4.1. Case definition and symptomatic assessment

One of the key weaknesses of the life events research, but similarly applicable to any systematic review in the medical sciences, is that when studies that cover a large period of time are considered, outcome measures are difficult to compare and could be outdated. In the case of first-episode research, Beiser et al. (1993) have previously commented that a “standardised, replicable method for establishing illness onset” (p.1349) does not exist, and that some criteria utilised in research studies may not be directly applicable to the DSM or ICD criteria used in clinical settings. However, although this may have been the case 20 years ago, a recent study suggests that the Screening Schedule for Psychosis (Jablensky et al., 1992), which is used in many psychosis studies, (including in this thesis) has good sensitivity and specificity (Morgan et al., 2012). In a large national survey, 90% of individuals who screened positive with this research tool were found to meet full ICD-10 criteria for a non-organic psychotic disorder (Morgan et al., 2012). Additionally, it is worth noting though that American diagnoses have changed dramatically from being much broader than the UK diagnostic criteria before 1980 to subsequently being much narrower. With this in mind, researchers should be mindful when reviewing and comparing some of the older US studies, and indeed, any studies that use different criteria to assess caseness and symptomatology.

The most common way that life event studies have defined caseness is through admission to psychiatric hospital. Even though many studies have used this method as a way of case definition, it is not without fault as the criteria for inpatient admission can be variable. The admission procedure may also not be a reflection of the level of psychotic symptoms currently being experienced, but rather show the need to manage harm to self and others, or due to a lack of support for that individual within their local community. Research supports the idea that recruiting solely inpatients is unlikely to paint a representative picture of individuals experiencing a first-episode of psychosis, as an early intervention service in Melbourne, Australia, reported up to one-third of their patients did not require inpatient treatment in the initial stages of their illness (Power et al., 1998).

With these limitations in mind, a sensible way to advance our methodology is to include a sample of incident cases that are drawn from both inpatient and outpatient community services. However, that said, not everyone with a psychotic disorder will present to mental health services when they start experiencing symptoms, and so even with this methodological improvement, some representativeness will be compromised as those who present to services are likely to be different from the individuals who do not seek medical advice. Another way to further improve comparability and generalisability to clinical settings, is to include standardised diagnostic tools and measures of symptoms, such as the OPCRIT which generates information about symptoms dimensions and leads to reliable diagnostic decisions, comparable to DSM and ICD diagnoses used in clinics (Brittain et al., 2013).

2.4.2. Objective ratings

The question of objective vs. subjective assessment of life events is one that has previously been extensively discussed in the literature (e.g., Dohrenwend et al., 1987b; Brown & Harris, 1989b). The primary problem with subjective evaluations of events is that these can be affected by mood and emotional state (i.e., by the very outcomes of interest) (Brown, 1974; Brown & Harris, 1989b). Given this, using subjective measures would make it impossible to distinguish cause and effect, and this is why most researchers have settled on objective measures. Furthermore, objectively rated interviews could be more complete in allowing consideration of various cultural or social factors, such as age or ethnicity, on the impact of events (Lazarus, 1999).

Further support for objective ratings comes into play when subjects are interviewed shortly after hospital admission or referral to psychiatric services, when their symptoms are likely to be at their most severe. In this context, their symptoms could influence the responses given on a life events interview. In some instances, studies have tried to minimise this issue by recruiting an informant, usually a family member, to verify the information provided by the patient (e.g. Brown et al., 1973; Tennant et al., 1979; Brown & Harris, 1982). However, family members could also be prone to recall difficulties or might simply not be aware of the intricacies of the events their relative has recently experienced or may not know of events at all.

If studies do measure the severity of events using subjective ratings, they should consider the impact of ‘effort after meaning’. This refers to the potential for participants

to attribute causality or otherwise unintentionally bias their responses in an attempt to understand what has happened to them (Bartlett, 1932). Inevitably, as the time passes before these events are discussed in the assessment, individuals may place inappropriate emphasis on certain events, while downplaying the impact of others. This is why I consider the most comprehensive method of determining event severity is based on an objective rating and corroborated using a consensus process. Although, unless these ratings are conducted blind to case status, an objective rating may also not be immune to the problem of ‘effort after meaning’.

2.4.3. Recall bias

Many of the limitations of the retrospective life events and psychosis studies are common to retrospective research in general. The key limitation is the reliance on participants’ memories of events that occurred up to a year prior to onset (which could well be many years previously). Paykel (1997) suggests that the memory of a major life event is usually restricted to the previous one year, which tends to be the minimum amount of time required by a life events interview (for case subjects). The presence of active symptoms could also make recall unreliable because of cognitive impairments associated with this illness (Heinrichs & Zakzanis, 1998). Researchers should also consider that when using a case-control design with a non-psychiatric comparison group, the recall of the patients may be more impaired than the controls and that any differences found may be reflective of a difference in recall, rather than an actual difference in recent stressors. Such a bias would typically reduce the likelihood of individuals with psychosis being identified as having had more recent stress, due to their poorer cognitive functioning, especially memory recall.

A second potential bias would work the other way, and would potentially identify too many recent stressors for first-episode cases. This would result in an ‘effort after meaning’ effect, as previously described above. However, as stated before, this could be minimised by using an informant and objective ratings of events. There is another issue with recall, as discussed by Day et al. (1987), in which patients tend to recall events as having occurred much closer to onset than is actually true in an attempt to find reasons to explain the onset of their illness, known as the ‘telescoping effect’. Again, this is something that could be minimised through the use of an informant, or it could be better be dealt with through the use of longitudinal studies using repeated

measures over time. However, even with these parameters in place, researchers must be realistic that no life events interview will ever be completely free from bias.

2.4.4. Independence

Many life events may actually be caused, at least in part, by behaviours and symptoms that often accompany the prodromal period prior to onset of psychotic disorders (i.e. those categorised as ‘dependent’ life events). Subsyndromal experiences of suspiciousness, apathy, and social withdrawal, for example, can often contribute to the occurrence of negative life events, and therefore, some experiences of dependent life events could plausibly be results of a developing disorder, rather than causally influencing onset (or the relationship could be, and perhaps more likely is, bidirectional). Therefore, event independence could be considered as a way of isolating the potential causal role of life events on psychosis onset, by distinguishing events that are independent of emerging symptoms.

As discussed, if the life events which precede an episode of psychosis are shown to be independent of emerging illness, then this strengthens the *hypothesis* that events have a causal impact on the onset of psychosis, rather than being caused by characteristics of prodromal illness. However, even if research suggests a propensity for dependent events to increase the odds of psychosis, then these findings should not be ignored. The finding of an abundance of dependent life events prior to onset could highlight (potentially modifiable) factors which may trigger a prodromal phase to turn into a first episode of psychosis.

When considering the independence of events, it is also important to take the timing of events into account. Exposure to an abundance of independent events close to the start of the onset period does strengthen aetiological implications. Furthermore, if this is supported in a case-control design, whereby independent events are more prevalent in cases than in non-psychotic controls, then an aetiological contribution of events is a stronger possibility.

2.4.5. Intrusiveness

There have been suggestions in the literature that certain types of stressors show specificity for psychosis and make individuals particularly vulnerable to developing

these disorders. However, in terms of particular life event types, no real trends have emerged out of the studies to date (e.g. Brown & Birley, 1968; Jacobs & Myers, 1976). One explanation for this is that researchers have searched for relationships between event categorisation and psychosis at a literal level, rather than considering a broader, perhaps more meaningful, psychological level.

Tirril Harris (Harris, 1987) considered the possibility of this broader construct and has provided support for the concept of ‘intrusiveness’. Intrusiveness refers to the unwanted interference and/or attempted control of an individual’s personal boundaries, usually by people or organisations outside of the individual’s personal network, and includes events such as a physical assault or being arrested. Exposure to intrusive events has been suggested to create feelings of paranoia which then increase the risk of developing a psychotic disorder (Harris, 1987). Harris (1987) reanalysed the Brown and Birley (1968) study and found the individuals with schizophrenia reported twenty times the amount of intrusive events when compared with controls (20% versus 1%), in the three week period prior to onset of symptoms. These intrusive events included burglaries, attacks, visits by the police, and communications by the bureaucracy or workplace management, all of which were intuitively identifiable as possessing a paranoia-stimulating quality. Although Harris was unable to report separate findings for the first episode patients (as this was a mixed first-episode and non-first-episode study), it is plausible that intrusiveness impacts on onset and on relapse as no differences were found between these two groups regarding other event characteristics. Furthermore, research has shown that traumatic childhood events which involved intention to harm, i.e. a characteristic of intrusive events, are particularly associated with a higher risk of psychotic symptoms (Arseneault et al., 2011; van Nierop et al., 2014), and so it is conceivable that (further) exposure to intrusive experiences in adulthood would also impact on the onset of psychosis. Clearly, intrusiveness is a concept which warrants further investigation.

2.4.6. Interactions with specific demographic factors

A few studies have considered the impact of demographic factors, e.g. age, gender and social class on the relationship between life events and the onset of psychosis, to see whether demographic factors modify the strength of the life event-onset relationship. Researchers have proposed that certain demographic factors could

play a part either because they affect the nature of the disorder itself, e.g. due to the process of aging, or perhaps because certain groups may be more prone to psychotic reactions in response to social stressors (Bebbington et al., 1996). Another process, termed ‘swamping’ may also be playing a role, whereby certain characteristics are associated with other disadvantageous factors which increase the risk for psychosis and overrule any effect of life events, thereby confounding the relationship between events and psychosis (Bebbington et al., 1996). Or possibly, some factors, e.g. social class, increase vulnerability to psychosis after adverse events by limiting access to the practical and emotional resources that encourage effective coping (Bebbington et al., 1996). However, it should also be noted both of these processes are likely to occur when considering demographic factors, and are not mutually exclusive. A consideration of the demographic distribution of stressful life events is important because it should help to identify groups who are at greatest risk from particular types of events, and therefore guide future research priorities and preventative efforts.

The next section will summarise some of the main papers which have assessed the impact of social variables on this relationship, and will also draw upon research from wider fields, e.g. from different psychiatric diagnoses and early adverse experiences, in order to hypothesise what might be seen in this study.

Social class

One of the most obvious demographic correlates of stressful experiences is social class position, as within any society, individuals in low socio-economic groups, with relatively fewer material resources, have been found to live shorter and less healthy lives than those further up the social hierarchy (Marmot, 2004). In the seminal study of life events and depression, Brown and Harris (1978) found that increased rates of severe life events and difficulties over the one year period prior to the onset of depression were experienced by 57% of working-class women, compared with 39% of middle-class women living in southeast London. This study is supported by a host of others (e.g. Dohrenwend, 1973; Myers et al., 1974; Thoits, 1982; Weich & Lewis, 1998; Lorant et al., 2007), including a study by Bebbington et al. (1986) which found that events are more likely to be associated with an increased risk of affective disorder in individuals who were of a lower socioeconomic status (SES), and in other studies of depression. A higher prevalence of traumatic events in lower SES has also been shown to increase the risk of posttraumatic stress disorder (PTSD) (Breslau et al., 1991, 1998).

However, in terms of psychosis, the findings are a little less clear-cut. In a case-control study of life events and psychosis, Bebbington et al. (1996) found that the odds ratio for the association between severe life events and psychosis was similar in the two class groups, although perhaps greater in the lower SES group when events of any severity were considered. However, exposure to adversity in childhood as a result of low SES, including living in rental apartments (a socio-economic marker), single-parent households, parental unemployment, and receipt of social welfare, has been found to be associated with an increased odds of later schizophrenia, and suggests that the association between adversity and psychosis may be different according to SES (Wicks et al., 2005).

A potential association between social class, adversity and psychosis may arise as a result of two competing hypotheses: social causation vs. social drift. The social causation hypothesis proposes that psychosis develops as a result of low social class (Cooper, 1961), whereas the social drift hypothesis proposes that individuals with psychosis are more likely to migrate to low SES neighbourhoods as a result of their illness (Dohrenwend et al., 1992). However, in the intervening years since these ideas were proposed, contrasting evidence has emerged and a recent systematic review of the literature suggests that there is not enough evidence to support an association between parental social class and an increased risk of psychosis (Kwok, 2014).

Due to these conflicting findings, there may be some merit in trialling a new approach to analysis and considering how the combined effects of low subject social class and life events act on increasing the risk of psychosis. As the effects of life events and low social class have been found to independently increase the odds of psychosis, and due to the likely correlation between these two variables, it makes plausible sense to consider their combined effects on psychosis onset.

Age

In one sense, it is plausible to assume that life events will increase with age, perhaps as health begins to deteriorate, and one becomes more dependent on family and friends for support. However, it could also be theorised that experience improves coping, and therefore events have less impact with increasing age. The research literature suggests the rate of life events experienced declines steadily with age,

certainly into the 60s and then perhaps increases again as friends and acquaintances become ill or die (Bebbington et al., 1991; Norris, 1992).

The effect of age on the life event-onset relationship currently appears to be inconclusive, as a case-control study found that although younger cases (less than 25 years) reported far more events than controls (cases 56% vs. controls 8%), the confidence intervals for the different age groups were found to overlap considerably and so it could not be concluded that there were any significant age-related differences (Bebbington et al., 1996). However, a review of the distribution of stressful life events by various demographic factors suggests that both traumatic and other stressful events are consistently reported more by younger age group within adult samples (Hatch & Dohrenwend, 2007). Due to psychosis being associated with younger age (e.g. DeLisi, 1992), it is not unreasonable to expect a potential interaction between age, life events and psychosis.

Gender

There have been many studies across different psychiatric disorders which have found a higher risk of psychopathology amongst women who have experienced stressful and traumatic experiences compared with men. These differential gender effects have been found for disorders such as PTSD (Stein et al., 2000; Walker et al., 2004), social phobia (Chartier et al., 2001), anxiety (MacMillan et al., 2001), and alcohol dependence (Knopik et al., 2004)). In terms of PTSD, Stein et al. (2000) and Walker et al. (2004) found that women were more likely to develop this disorder than men despite being exposed to similar types of trauma. Furthermore, studies in the PTSD literature indicate there is consistently around a two-fold greater risk of the disorder amongst women exposed to trauma than men (Kessler et al., 1995; Breslau et al., 1997), and this effect is especially heightened for intrusive experiences such as physical assault and rape (Norris, 1992; Breslau et al., 1999).

In terms of psychosis, findings have been somewhat more mixed. In the Bebbington et al. (1993) study of life events and psychosis, female patients were found to have more life events than male patients prior to the onset of symptoms, but this was also found to be true of the control participants, and there was little difference in the association between events and onset between the two sexes. However, van Os et al. (1994) found that more females had experienced severe events prior to onset (56% of

women exposed to events prior to onset vs. 27% of women not exposed to events prior to onset), although these differences did not reach standard levels of statistical significance. More recently, Myin-Germeys et al. (2004) found that women had a significantly increased emotional reactivity to daily stress compared to men, and these affective changes may increase their risk for later psychosis (Myin-Germeys & van Os, 2007). In a recently published study, similar findings have also been found which suggest women may be more sensitive to increases in positive psychotic symptoms after exposure to traumatic life events (Gibson et al., 2014). Although other studies have also found a differential gender effect that is biased towards women (e.g. Lardinois et al., 2011; Oldehinkel & Bouma, 2011), not all studies have found gender differences (e.g. Myin-Germeys et al., 2001; Devylder et al., 2013).

On balance, it appears more likely that the association with psychosis after exposure to stress will be greater for women than men, with perhaps a more insidious onset of illness associated with men and a clearer event-related onset associated with women, although further exploration is still required.

2.5. Literature gaps and next steps

2.5.1. Literature gaps

Several design issues have yet to be (fully) utilised in the literature to date and these require replication and novel exploration. Firstly, in order to advance aetiological understanding of the role of life events in psychosis onset, there is a need for this to be tested using large case-control study designs. Of the previous studies to fully utilise this design (Brown & Birley, 1968; Canton & Fraccon, 1985; Al Khani et al., 1986; Dohrenwend et al., 1987a; Gureje & Adewunmi, 1988; Bebbington et al., 1993; Faravelli et al., 2007; Mondelli et al., 2010), only Bebbington et al. (1993) included a reasonable sample size with a comparison of 97 cases and 207 population-based controls. However, this study is limited in what it can tell us about aetiological effects of life events as the sample included a mixture of first-onset and relapsed patients. Few studies have used the gold-standard method of the LEDS (Brown & Harris, 1989a), and this was used by only one first-episode only case-control study (Faravelli et al., 2007), but the psychosis patient sample in this study ($n=9$) was too small to allow for any meaningful analyses. Furthermore, none of the previous clinical studies measured and

adjusted for other risk factors over and above basic demographics, e.g. drug use; or gave a consideration to potential pathways from life events to psychosis.

Issues of event type and severity have yet to be explored fully in a first-episode only design. Severity is an important consideration because, as discussed previously, it is more likely to play a part in onset than in subsequent relapse. Only two first-episode studies have considered the effect of event severity, as measured by the LEDS. Raune et al. (2009) found a large increase in moderate and severe life events (OR=5.0) three months prior to onset in cases compared with controls. However, as mentioned in the review paper, this study used a comparison group from studies conducted 20 years previously. Faravelli et al. (2007) found cases (n=9) to experience nearly three times as many severe life events prior to onset than controls (n=123), but due to the very small case sample, only very tentative conclusions can be made from these findings. With the lack of studies to investigate this concept prior to onset, a comparison of event severity in first-episode cases and population-based controls is still required.

In terms of the types of events that occur before onset, Raune et al. (2009) also started to consider further qualitative elements and reported the impact of intrusive events, showing that exposure to intrusive events in the three months prior to onset appeared to increase the odds of psychosis by seventeen times. However, this requires replication using a more robust case-control design as other than the Raune et al. (2009) study, the impact of intrusive events on psychosis onset has yet to be investigated in a published study, despite researchers hypothesising their potential aetiological importance (Harris, 1987).

Another consideration that has not been investigated within the psychosis literature is the impact of chronic difficulties on the onset of disorder. Although the LEDS probes for this information, to our knowledge, no study so far has investigated this in individuals with psychosis and only a handful have looked into this in depressive illnesses (e.g. Farmer & McGuffin, 2003; Husain et al., 2012; Traviss et al., 2013).

2.5.2. The next generation

The main aim of the present study will therefore be to gain a more thorough understanding of the impact of life events and difficulties in the year period before a first episode of psychosis, and to start to unpick some of the potentially targetable social

and psychological pathways that may link life events to psychosis. In order to better understand the nature of the link, if any, between life events and psychosis, there is a need for a new generation of studies which improve upon some of the previous methodological weaknesses and aim to minimise recall and selection biases. Concern with addressing prior limitations has informed the design of this study (see Chapter 4-Methodology).

2.6. Summary of Chapter 2

This chapter has discussed the impact of stressful events in adulthood and its relationship with psychosis onset. It is important to gain an improved understanding of this association because a consistent link would suggest clinical gains could be made from targeting this link directly, or the potential biopsychosocial pathways that are likely to be linked with illness onset. Revealing a sound link between exposure to life events and psychosis onset could also lead to theoretical advancement and strengthen models of aetiology; and methodologically, the first episode represents a useful opportunity to further understand aetiology without the addition of potential confounding variables, such as chronic medication use and cognitive deterioration.

The review and meta-analysis identified a surprisingly small number of research studies ($n=16$), which spanned over 40 years of research, and assessed the impact of recent events on the onset of psychosis or subclinical symptoms. The majority of the studies supported an association between life events and psychosis onset and the weighted odds ratio from the meta-analysis suggested a three-fold increase in the odds psychosis after exposure to recent life events. Events appeared to be occurring at an increased rate in the year prior to onset, compared with the year period prior to interview for controls, and there was an increase in independent events which are outside of the individual's control. Life events of a severely threatening nature appeared to have a stronger impact on psychosis onset compared to less severely threatening events, and there is also some tentative evidence of intrusive event specificity for psychosis, which requires further testing. Although a confident effect size of the impact of events on psychosis onset is difficult to estimate, there are indications that the association may be of clinical and theoretical significance.

However, many of the studies to date are plagued by methodological weaknesses and we must be careful in drawing any inferences about the aetiological

role of life events in psychosis because much of the existing research was found to be methodologically limited, with issues such as, cross-sectional designs, lack of careful dating of events and onset, lack of first-episode only studies, lack of comparison groups, and the use of checklist measures of events.

Key conceptual and methodological considerations to bear in mind when wanting to gain an understanding of whether life events are aetiological relevant for psychosis are the use of incident cases and an appropriate, randomly selected control group drawn from the same population as cases; standardised method of symptomatic assessment and a standardised method of case definition; limitation to cases where it is possible to date onset accurately; precise dating of events to identify the salient period of interest; and an objective rating of the impact of events, including an objective assessment of event independence.

The present study aims to gain a more thorough understanding of the impact of life events and difficulties proximal to the onset of psychosis. This study includes various design features which both address the methodological limitations of previous studies and also answer some new questions. These questions include uncovering the specificity of event types prior to psychosis onset, with a particular focus on analysing the intrusiveness-psychosis link, which goes far beyond the work of previous literature.

CHAPTER 3 - Psychological Pathways from Social Adversity to Psychosis

Synopsis

Recent models of psychosis implicate stressful experiences in its aetiology, and these experiences may increase the risk of onset via mediating and moderating variables, such as cognitive and affective processes. However, these assertions are mostly theoretical in nature, and the mechanisms involved are not supported by a large body of empirical studies. This chapter identifies and critically evaluates the studies that have investigated the role of specific psychological mechanisms in the relationship between adversity and psychosis, and sets up a justification for the analyses explored later in this thesis. The chosen mechanisms were guided by contemporary cognitive models of psychosis and included affective pathways (e.g., symptoms of depression and anxiety) and negative core schemas. Very few studies have considered the possible psychological pathways between stressful experiences in adulthood and the onset of psychotic disorders; therefore this chapter covers research that has looked at a variety of stress exposures, including childhood and adult adversities experienced prior to the onset of psychotic experiences.

3.1. A direct pathway?

There are a number of ways in which experiences of adversity may lead to the development of psychosis, and one possibility that has been proposed is that of a direct pathway between adversity and psychosis. It has been suggested that positive psychotic symptomatology, such as hallucinations or delusions, could be reactions to severe adversity, especially when the content of these symptoms mirror the themes of the traumatic event previously experienced (Reed & Argyle, 1999; Hardy et al., 2005; Longden et al., 2011). The arousal experienced after a threatening event is thought to have a direct effect on memory processing (Brewin et al., 1996; Ehlers & Clark, 2000), whereby the ability to form detailed memories is reduced, but the encoding of associative memories becomes heightened. After the traumatic experience has occurred, and sometimes a long while after, these memories can be involuntarily invoked by stimuli associated with the trauma and can transform themselves as vivid hallucinations or other psychotic-like phenomena which take the form of direct expressions of previous trauma memories. This type of memory process is thought to underlie the re-experiencing symptoms in posttraumatic stress disorder (PTSD), but has also been

suggested to be potentially relevant for psychotic disorders (Hardy et al., 2005). However, a key difference is that for some individuals with psychosis, this re-experiencing of trauma memories may not be attributed to the previous exposure, but instead to an external agent.

A direct link between stressful experiences and psychosis has been assessed in relation to severe trauma exposure, as well as potentially less threatening adult experiences. In terms of severe traumatic experiences, Hardy et al. (2005) found that 12.5% (n=5) of a sample of 40 individuals who had experienced PTSD-threshold trauma prior to a relapse in psychosis, experienced hallucinations with similar content to their previously experienced traumas. Intrusive traumatic events, such as sexual abuse and bullying were shown to have the strongest associations with subsequent hallucinations. However, it was also found that 42.5% of the sample did not have an identifiable association between their symptoms and prior traumatic experiences, suggesting that other factors are likely to contribute to the occurrence and nature of hallucinations. It is also possible that an individual will start out by experiencing flashbacks which eventually morph into unconnected hallucinations; thereby PTSD symptoms could mediate the adversity-psychosis association as well.

More congruence between a patient's life events and the content of their symptomatology has been found by Raune et al. (2006), who reported some association between the themes expressed in delusions and auditory hallucinations and the characteristics of stressful events prior to onset. They found that 73% of their sample (n=30) who developed persecutory delusions or hallucinations, had experienced intrusive events in the twelve months prior to onset. However, due to the heterogeneous nature of psychosis, many of the subjects had overlapping symptoms, and exposure to different events, which can contain different attributes within one single event, e.g. intrusiveness and loss. Therefore it is not possible to say with any confidence that a particular event attribute influenced a particular symptom.

The partial congruence shown above between the nature of adverse experiences and the form and content of psychotic symptoms suggests that there may be a causal link. However, an alternative view would be that psychotic symptoms are always coloured by cultural themes and life histories. And so if an individual's life has contained traumas, this will be used in their development of explanations for anomalous experiences, and thus the content of their symptoms will be drawn from experience. Therefore, with this viewpoint, the fact that for some individuals, traumatic experiences

intrude into their hallucinations and delusions, is not necessarily evidence of a causal connection.

3.2. Indirect pathways

An alternative viewpoint is to see the stress-psychosis link as being influenced by a combination of mediating and moderating factors, and therefore these two variables are indirectly connected to each other via other intermediary or precipitating factors. Many indirect pathways between stressful experiences and the development of psychosis have been proposed, and these have been considered within contemporary aetiological models of psychosis (e.g. Morgan et al., 2010; van Os et al., 2010; Howes & Murray, 2014), as well as the more psychologically orientated cognitive models of psychosis (e.g. Fowler, 2000; Bentall et al., 2001; Garety et al., 2001, 2007; Morrison, 2001; Freeman et al., 2002). The following section of this chapter will introduce one of the key cognitive models of positive psychotic symptoms proposed by Garety et al. (2001, 2007), from which specific pathways have been drawn and tested within this thesis.

3.2.1. Cognitive Models of Psychosis

Cognitive models of psychosis attempt to explain the cognitive, social and affective processes that contribute to and maintain an episode of psychosis, and a number of models have been proposed over the last decade (e.g. Fowler, 2000; Bentall et al., 2001; Garety et al., 2001, 2007; Morrison, 2001; Freeman et al., 2002). The key features that they share are that pre-existing beliefs or schemas and ongoing appraisals are essential for the onset and maintenance of psychotic experiences. One of the most recognised, contemporary cognitive models of positive psychotic experiences, such as hallucinations and delusions, is that of Philippa Garety and colleagues (Garety et al., 2001; Garety et al., 2007). The model extends earlier theoretical ideas as Garety et al. (2001) argue that it combines disturbances in automatic cognitive processes and negative appraisals; it covers delusions and hallucinations under one framework; it proposes a significant role for emotion; and it considers the way in which social factors may contribute to the aetiology, maintenance or relapse of symptoms. The model also encourages the generation of testable hypotheses and was intended to lead to theoretical and therapeutic advances (Garety et al., 2001).

The cognitive model proposed by Garety et al. (2001, 2007) suggests two main pathways from social adversity to the development of psychosis. Firstly, the authors suggest the most common pathway to psychosis is one whereby exposure to social adversity further disrupts cognitive processes in a predisposed individual (Garety & Hemsley, 1994). Exposure to early adversity (such as childhood trauma) may result in the development of negative beliefs about the self (e.g. as vulnerable, weak and unlovable) and others (e.g. other people are dangerous or untrustworthy), in an individual that may be vulnerable to developing psychosis. These negative schema may have a direct effect on lowering self-esteem and lead to a tendency to attribute later adverse experiences (e.g. negative life events) to external causes, potentially giving rise to psychotic experiences (Freeman et al., 1998; Garety et al., 2007). Stressful life experiences can trigger other maladaptive cognitive and also later affective changes which could potentially lead to unusual perceptual experiences, such as hearing voices or sounds that are not really present. Garety and colleagues (Garety et al., 2001, 2007) propose these cognitive changes, including specific reasoning and information processing biases and pre-existing schematic beliefs about the self and others, affect the interpretation of the origin of the anomalous perceptual changes. These experiences are seen as having an external cause, which can increase distress and uncertainty, leading to their exacerbation and potential to develop into a psychotic disorder. For many individuals, the experience of voice hearing will not then lead to disorder, but it is the way that these experiences are evaluated by the individual, e.g. the experience is externally caused, it has some personal meaning and it is uncontrollable. These appraisals could increase distress and further exacerbate the experiences of psychosis.

Another pathway to psychosis that Garety and colleagues propose is one which includes a central role for affective disturbance (Garety et al., 2001). Exposure to adversity may increase levels of depression and anxiety, which then directly activates biased appraisals of their experience, and negative schemas about the self and others, leading to an external, delusional interpretation of their experiences. Adverse life events have been shown to be associated with depression and anxiety (e.g. Ventura et al., 2000; Fowler et al., 2006a) and these symptoms can lead to the later development of psychosis (e.g. Krabbendam et al., 2005; Freeman et al., 2011), and so it appears that research findings are, circumstantially, supportive of this potential pathway. Bebbington et al. (2011) suggest that a maladaptive predisposition of emotional dysfunction and negative schemas could provide a catalyst for an “automatic negative cognitive pathway”. As a result, the experience of further adverse life events may lead to unusual experiences and

emotional imbalance, which if appraised as external, may then lead to the symptoms of psychosis.

Another affective pathway from adversity to psychosis has also been proposed, but this pathway does not include any cognitive alterations (Garety et al., 2001). In their cognitive model, Garety and colleagues suggest that this mechanism may hold true for a small proportion of individuals with psychotic symptoms (e.g. some individuals with delusional disorder). For these few, it appears that a triggering event does not cause a basic information processing disruption prior to the development of anomalous experiences, and only leads to disturbed affect. For these individuals, Garety et al. (2011), suggest that the experience of delusions occur independently of hallucinations and other psychotic symptoms.

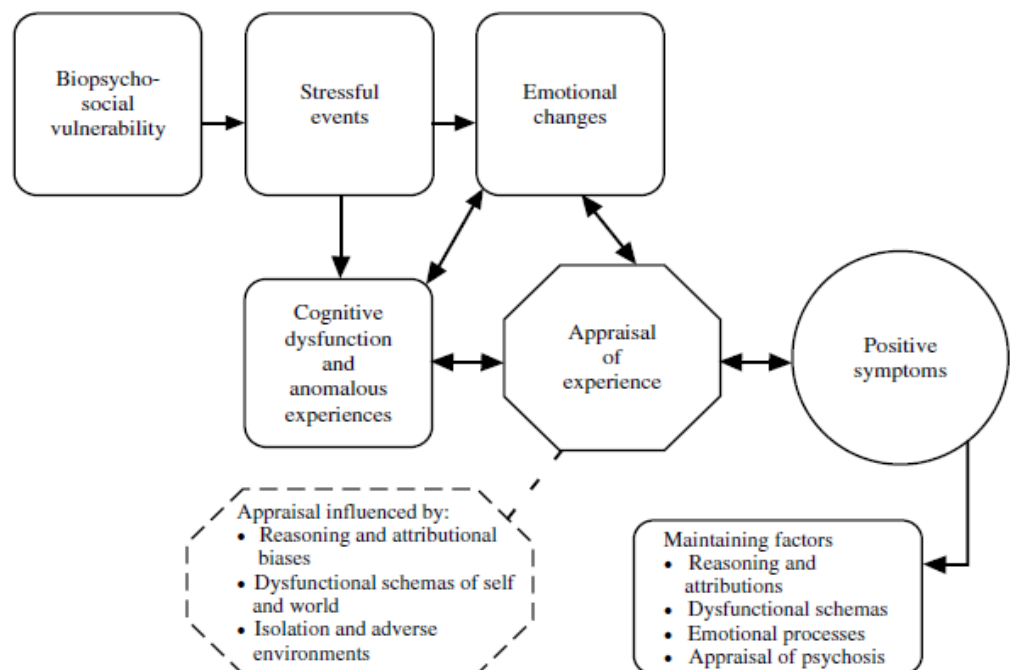


Figure 3.1 Schematic representation of a cognitive model of the positive symptoms of psychosis (taken from Garety et al., 2007)

3.3. Negative Schemas

The term ‘schema’ refers to the way an individual appraises themselves, other people and the world around them. It is a concept that has been studied for many decades (Beck, 1967; Beck, 1976). These constructs were originally discussed in relation to theories of depression (Beck, 1976; Teasdale & Barnard, 1993; Clark et al.,

1999), but have since been integrated into more contemporary theories of numerous psychiatric disorders, including PTSD (e.g. Ehlers & Clark, 2000), and eating disorders (Fairburn et al., 2003). Negative schemas about the self and others have also been incorporated into several models of psychotic symptoms, such as paranoia and persecutory delusions (Chadwick et al., 1996; Bentall et al., 2001; Freeman et al., 2002), hallucinations (Beck & Rector, 2003) and delusions (Fowler, 2000; Garety et al., 2001, 2007). However, researchers suggest that an understanding of the exact nature and significance of the schema construct is lacking and that different cognitive theories propose conflicting hypotheses (Fowler et al., 2006b).

Research suggests that schemas are formed early in life and remain stable throughout adulthood (Young, 1999) and these evaluations are likely to form part of a basic human response to stressful or threatening experiences (Fowler et al., 2006b). Early adverse experiences are proposed to create an enduring cognitive vulnerability, characterised by negative schematic models of the self and others (e.g. I am worthless, others are dangerous), and then further along the life-course, these negative beliefs are thought to underlie the mistrust and suspiciousness associated with both the development and maintenance of paranoid thought processes (Freeman et al., 2002). In particular, the underlying sense of threat associated with negative beliefs about others is argued to form a crucial part of the threat beliefs which are integrated into the paranoid cognitions (Freeman et al., 2002).

Cognitive models also propose that when an individual experiences subsequent adversity, negative schemas about the self and others are likely to become re-activated, which can increase levels of negative affect and influence appraisals of anomalous thoughts and behaviours. In combination, these affective and cognitive changes elicited by the stressful experience have been theorised to increase the risk of psychotic symptomatology (Garety et al., 2001; Freeman et al., 2002).

In order to advance research in this area, Fowler et al. (2006b) created the 'Brief Core Schema Scale' (BCSS) to assess individuals' beliefs about the self and other people. The authors aimed to develop a scale that would provide a quick and easily administered measure of negative evaluations of self (negative self-schema) and others (negative other-schema), but also of positive evaluations of self (positive self-schema) and others (positive other-schema). The BCSS has been shown to be a more reliable construct than traditionally used self-esteem measures and more independent of mood (Fowler et al., 2006b). Mixed findings exist surrounding the relationship between self-

esteem and paranoia but Freeman (2007) argues that specific negative schemas about the self and others are more likely to play a role in the development and maintenance of these symptoms. Research using this scale has found that negative appraisals of self and others are associated with psychotic symptomatology, especially delusional thinking, in both clinical and non-clinical populations (Fowler et al., 2006b; Smith et al., 2006; Gracie et al., 2007; Steel et al., 2009; Fowler et al., 2012); and has been shown to be a sensitive enough trait that can differentiate patients from controls (Fowler et al., 2006b).

The following section of this chapter will present research looking at whether the presence of negative schemas mediates the relationship between adversity and psychosis onset. Cognitive behavioural therapists have reported that in people with psychosis it is often possible to link extreme negative self-evaluations to early interpersonal trauma, predating the onset of illness (Fowler et al., 1995), and thus, it seems plausible that negative schemas may act as a mediator in this relationship between early trauma and the development of adult psychosis.

3.3.1. Schemas as a mediator between adversity and psychosis?

Since the publication of Garety and colleagues (2007) theoretical paper, research has sought to test the hypotheses of this cognitive model of psychosis and has so far confirmed its predictions. Although mediation research in this area is scarce, it points towards negative core beliefs as a possible mediator between trauma exposure and the development of psychotic experiences. Using a general population sample of 228 students recruited via an email circular, Gracie et al. (2007) investigated the relationship between lifetime trauma exposure and predisposition to hallucinations and paranoia in a non-clinical sample. Through the use of computerised versions of questionnaires accessed by participants via a webpage, the authors measured exposure to traumatic events across the lifetime, akin to those which meet the definition of a 'traumatic stressor' in relation to PTSD diagnostic criteria. They also measured experiences of emotional abuse, neglect and bullying in childhood. The majority of participants ($n=202$, 88.6%) reported experiencing at least one traumatic event at some point in their lifetime, and the mean number of events experienced was found to be 3.6 ($SD= 2.8$), with women (4.11, $SD= 2.94$) experiencing more events than men (mean= 2.55, $SD 2.22$). Paranoia was found to be strongly associated with all types of traumas experienced, and the overall number of traumatic events experienced. The authors found

a strong association between negative schemas and paranoid thinking. High correlations were found between paranoia and negative schemas, and negative beliefs about the self and others were found to contribute to 29% and 32% of the variance in paranoia, respectively. These associations remained strong when all variables were entered into the standard multiple regression. Overall, these results supported the prediction that the pathway from trauma to paranoia may be mediated by negative schematic beliefs. The authors also found that PTSD re-experiencing symptoms were found to be most strongly associated with a predisposition to hallucinations, which suggests that PTSD re-experiencing symptoms might mediate the relationship between trauma and hallucinations. Gracie and colleagues suggest that their results provide support for two pathways between trauma and the development of psychotic experiences, but these pathways may not be mutually exclusive, and there may well be interactions between the two. However, as the design was a retrospective, cross-sectional study, the conclusions concerning any mediation effects must be treated with caution. Furthermore, participants were recruited via the Internet which could inflate selection biases and the non-clinical sample limits the generalisability of these results to clinical populations.

A more recent study also suggests that these psychological pathways are involved in the relationship between trauma and psychosis. By specifically investigating pathways to psychosis after exposure to childhood adversity, Fisher et al. (2012) extended research assessing negative schemas as a potential mediator, and improved upon the previously discussed study by ensuring that the associations found were less likely to be the product of reverse causality. Using a general population sample of 212 adults, Fisher et al. (2012) retrospectively assessed the severity of emotional, physical, and sexual abuse, and emotional and physical neglect experienced prior to 17 years of age, and also assessed the experience of paranoia in the past year, and the presence of negative schematic beliefs. Over a quarter of the sample reported exposure to physical neglect and emotional abuse during childhood and a third of participants reported experiences of paranoia in the past year. Negative self-beliefs were found to partially account for the associations between emotional and physical abuse in childhood and adult paranoia, although both indirect pathways fell short of standard statistical significance levels. Although these findings suggest that negative schematic beliefs about the self are involved in the pathway between childhood trauma and the development of paranoia in adulthood and support the theoretical propositions of a

cognitive model of psychosis (Garety et al., 2001), the trauma-paranoia associations were not fully mediated in this sample, suggesting that other factors are likely to also be involved in these pathways. As with the previous study, the generalisability of these findings is limited by the use of a self-selecting and non-clinical sample. Furthermore, although the trauma being disclosed occurred prior to the recent experiences of paranoia, the cross-sectional design prevents any confident assertions of mediation.

Another recent non-clinical study has tested these theory-driven cognitive factors and made use of a prospective design to see whether negative schemas predicted self-reported paranoia six months after exposure to a physical assault (Freeman et al., 2013). Freeman and colleagues assessed 106 adults who had attended A&E services due to injuries sustained after experiencing a physical assault. The participants were assessed at one month (baseline), and then again at three months and six months after hospital attendance, and were measured for a variety of factors, including their levels of paranoia, affective symptoms, and presence of negative schemas. The authors found that negative beliefs about others at baseline (one month post-assault) predicted later paranoia at the final follow-up assessment (six months post-assault), providing some support for the role of negative schemas about others as a mediator in the relationship between interpersonal trauma and later paranoia. However, there may be an alternative explanation as the authors did not find much of a decline in the levels of paranoia reported across the follow-up period. It may therefore be possible that some of the participants already had high levels of paranoia prior to the assault, and therefore an explanation in terms of mediation does not apply. Furthermore, as the design did not allow paranoia to be measured prior to the assault, it is impossible to say with any certainty that the assault led to an increase in paranoia. Alternatively, the findings could be interpreted as showing that the impact of a physical assault contributes to a longer lasting impact on people's levels of trust for others, and indeed, the majority of subjects viewed their assault as responsible for increasing their suspiciousness.

3.3.2. Schemas as a causal partner?

To our knowledge, there are no published studies which have assessed the potential synergistic effects of negative schemas in the trauma-psychosis relationship. As discussed previously, schemas are likely to have formed early in life as a result of childhood experiences, and can be re-activated in the event of adversity further down the life-course. If individuals develop psychotic symptoms following adverse adult

experiences, then it makes theoretical sense that the re-activation of negative schemas acts as a causal partner together with adult adversity to increase the risk of psychosis. With this in mind, exposure to adult life events which cross a severity threshold could increase some individuals' risk for psychosis due to the activation of negative schemas. However, without support from empirical research, we cannot make any confident hypotheses about the size and direction of this effect. This thesis will take an exploratory approach to see whether analyses support these propositions from the cognitive models.

3.4. Affective Pathways

In an editorial concerning the use of CBT for psychosis, Birchwood and Trower (2006) argue that emotion and psychosis were “divorced” from each other in the mid-20th century in a movement led by Karl Jaspers. Jaspers (1963) proposed that there should be a divide between affective illness and “madness proper”, and the two were distinctly unconnected, with psychosis and neurosis being studied and treated independently of each other (Freeman & Garety, 2003). However, a revival and “remarriage of emotion and psychosis” (Birchwood & Trower, 2006) is well underway, and researchers recognise that the role of affective processes in the development and maintenance of psychotic symptoms is an important one (e.g. Birchwood, 2003; Freeman & Garety, 2003). Research suggests that negative emotional states, including experiences of depression and anxiety, are thought to contribute to the development of positive psychotic symptomatology, such as paranoia, delusional thinking and hallucinations (Smith et al., 2006; Freeman, 2007; Bentall et al., 2008; Freeman & Fowler, 2009). In their cognitive model of persecutory delusions, Freeman et al. (2002) consider persecutory beliefs as an extension of anxious and depressive worries about an individual's own vulnerability and lack of worth, and postulate that these maladaptive emotions are likely to be present prior to the development of psychotic symptoms.

Negative affective states may form the beginning of a causal pathway to psychosis as researchers have found that depression and anxiety increase the risk for developing psychotic symptoms, and are strong predictors of transition to disorder (Jones et al., 1994; Krabbendam et al., 2005; Owens et al., 2005). Further research from robust experience sampling studies that have utilised clinical samples have also found that increases in anxiety predict the occurrence of paranoia (Ben-Zeev et al., 2012), and

there is also some tentative evidence that experimentally increasing anxiety via a display of anxiety evoking pictures, leads to an increase in paranoid thoughts (Lincoln et al., 2010). Consistent with these findings, psychotic-like experiences have also been found to be more common in individuals with anxiety and depressive disorders (Varghese et al., 2011).

Not only is there a clear relationship between affect and psychosis, affective changes are also likely to be linked to the experience of adversity which often predates the onset or relapse of psychotic symptoms. Research suggests that the experience of adversity can lead to negative affective changes, and supports the theoretical suggestions described previously, of a pathway from adversity to psychosis via negative affect. Indeed, evidence suggests that affective processes, adversity and psychosis are likely to be interlinked. For example, Bendall et al. (2011) found that patients with psychosis who had been exposed to trauma in childhood reported more depressive symptoms than those not exposed to childhood trauma, and Ventura et al. (2000) showed that the experience of stressful events in adulthood was associated with an increase in both depressive and psychotic experiences in patients with schizophrenia. However, research is lacking which focuses on better understanding the temporal order of these processes, and the following section of this chapter will evaluate research that has attempted to do this by assessing the role of affective state as a mediator between adversity and psychosis.

3.4.1. Affective state as mediator between adversity and psychosis?

Freeman and Fowler (2009) have reported a role for anxiety in mediating the relationship between trauma and psychosis in a general population sample. Using a cross-sectional design, 200 adults completed self-report questionnaires that measured exposure to severe trauma across the lifetime, and experiences of verbal hallucinations and paranoia, negative self-beliefs, and levels of depression and anxiety. The analysis only included events that satisfied the severity criterion related to a PTSD diagnosis. Experience of at least one traumatic event during the lifetime was reported by 70% of the sample (n=140), with 25.5% experiencing childhood physical or sexual abuse (n=51), and 15% experiencing a traumatic event in the last year. In terms of psychotic-like experiences, paranoid ideation was reported by 115 subjects (57.5%), and verbal hallucinations were reported by 31 subjects (15.5%). Being exposed to at least one traumatic event was associated with a 2.5 times greater risk of reporting persecutory

thoughts than those who did not experience any traumatic events, and a 4.8 times greater risk of reporting verbal hallucinations. Exposure to a minimum of one traumatic event was also associated with higher levels of depression and anxiety, and similarly psychotic experiences were associated with these affective symptoms. After finding these associations, the authors tested whether the affective processes mediated the relationship between trauma and psychosis. Anxiety, but not depression, was found to be a statistically significant predictor of paranoid ideation and also of verbal hallucinations; indicating that trauma could influence persecutory thinking via the creation of anxiety. However, clearly, the cross-sectional study design weakens these mediation claims as the direction of causality remains unclear.

As well as assessing the potential mediating effect of negative schemas, the Fisher et al. (2012) paper mentioned previously also looked at affective processes as a mediator between childhood maltreatment and paranoia. The authors measured current depressive symptoms and current anxiety levels over the past week. Both levels of anxiety (OR= 3.87) and depression (OR= 3.52) were associated with experiences of paranoia in the past year; however, only anxiety emerged as a potential mediator between childhood maltreatment and later paranoia in this sample. Of all the pathways assessed, the only one to reach conventional statistical significance levels (and only just) was the pathway between emotional abuse, anxiety and paranoia, and there was a trend seen for an indirect pathway between physical abuse, anxiety and paranoia. It is interesting that depression was not found to be a mediator between childhood maltreatment and paranoia in this sample, suggesting that anxiety may have some specificity for influencing experiences of paranoia, and perhaps depression is more closely linked to other psychotic symptomatology, such as hallucinations (e.g. Krabbendam et al., 2005). However, as said before, we cannot be sure that what we are seeing are true mediation effects due to the cross-sectional design, and the fact that paranoia could well be present prior to the development of affective symptoms.

Other researchers have also tested the association between childhood abuse and psychosis, and assessed whether the relationship is consistent with mediation by anxiety and depression. Using data from the Adult Psychiatric Morbidity Survey of 2007 (McManus et al., 2009), Bebbington et al. (2011) made use of a representative general population sample of 7353 adults (aged 16 years and over) in England. The participants were assessed for their experiences of sexual abuse in childhood (prior to 16 years), and their current levels of anxiety and depression (in the past week). A two-stage screening process was also used to identify individuals with probable psychotic disorder, of whom

38 (0.5%) individuals screened positive. When anxiety was added to a model of childhood contact sexual abuse (experiences of either sexual touching or non-consensual intercourse), and probable psychosis, the addition of the anxiety score reduced the effect of abuse on psychosis considerably, with the odds ratios reducing from 3.5 (95% CI 1.8-6.8) to 2.3 (95% CI 1.1–4.8). Furthermore, when depression was considered as a potential confounder, the odds ratio between contact abuse and psychosis fell just short of standard significance levels (OR 2.2, 95% CI 0.9–5.0). When the two affective processes were considered together in a single analysis, the association between contact abuse and psychosis did not become much stronger (OR 2.4, 95% CI 1.1–5.2). Evidence of partial confounding was also seen when considering just non-consensual sexual intercourse in childhood. The addition of anxiety and depression both substantially lowered the odds ratios between abuse and psychosis (from 10.0 to 5.8, and to 4.1 respectively). As before, analysing the two affective processes together did not dramatically alter the results (OR 4.2, 95% CI 1.7–10.7). These analyses suggest that anxiety and depression partially confounded the relationship between childhood sexual abuse and psychosis; both when considering contact abuse as a whole, and with non-consensual intercourse separated out. The authors note that there is also a possibility that depression may be more central to this model than anxiety as when both affective processes were considered together, the effect of anxiety was no longer statistically significant. It would be interesting to see if this result is replicated in other samples and if so, begin to theorise as to why this may be the case.

While the majority of studies so far have been limited by a cross-sectional design which impedes any temporal relationships from being accurately established, Fisher et al. (2013a) utilised a longitudinal design of a large sample of children to see whether associations between victimisation and psychosis were mediated by affective processes. Prospective data was available on a sample of 6692 children from the UK Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. In terms of trauma assessments, these included maternal reports of domestic violence and parental hostility in early childhood, and the children themselves reported on experiences of bullying prior to 8.5 years. Affective processes were measured by maternal report of their children's current anxiety levels at 10 years and their depressive symptoms at 9 and 11 years. Psychotic experiences over the previous six months were asked about from the children directly at a mean age of 12.9 years. There were 790 children (11.3%) who reported probable or definite psychotic symptoms ('broad') that were not due to sleep, fever, or substance use and 315 (4.7%) were considered to only have definite symptoms

(‘narrow’). The authors found that the association between harsh parenting and broadly defined psychotic symptoms was partially mediated by anxiety (17% mediated) and depressive symptoms (47% mediated). Affective processes also partially mediated associations between ‘broad’ psychotic symptoms and bullying (anxiety: 3% mediated; depression: 8% mediated), and also exposure to domestic violence (anxiety: 9% mediated; depression: 16% mediated). Interestingly, the mediating effects of the affective factors were broadly similar when considering both ‘broad’ and ‘narrow’ psychotic experiences. Despite the prospective design, the possibility of reverse causality cannot be completely disregarded as the variables were measured reasonably close together and the mediating variables and psychotic experiences were not additionally assessed prior to trauma exposure. However, as the authors note, it would be difficult to reliably obtain these measures at an earlier stage due to the age of the sample. Except for harsh parenting, the association between the other measured trauma exposures (domestic violence and bullying) and psychosis were not fully explained by the mediators of interest in this study (anxiety, depression, self-esteem and locus of control), suggesting that there are a range of other potential mechanisms that are likely to be involved in these pathways. It is also important to note that this study focused on psychotic experiences, which may not be exclusively linked to psychotic disorders (e.g. Fisher et al., 2013b), and therefore may have limited generalisability to clinically relevant disorders. However, these findings are nonetheless important, and tentatively suggest that specific affective difficulties in childhood could be targeted to minimise the risk of psychosis after exposure to early trauma.

Although not strictly looking at either depression or anxiety as a potential mediator, Marwaha et al. (2014) have considered the concept of mood instability as a mediator of child sexual abuse and psychosis. Using British national survey data from the 2007 psychiatric morbidity survey, 7403 adults aged 16 and above were assessed for the presence of probable psychosis, for the experience of sudden mood changes over the past several years and for exposure to childhood sexual abuse (involving either intercourse or physical molestation), prior to age 16. The authors found the mood instability mediated 34.6% of the total association of child sexual abuse with psychosis, 34.5% of the effect with paranoid ideation and 25.3% of the effect with auditory hallucinations. There are some limitations to this study, namely the use of a single question to assess for the presence or absence of the mood instability construct. With this question there was no way of distinguishing the severity of the mood disturbance within the participants, or how often it occurred and its average duration, and therefore

the individual experiences are likely to differ in several unaccountable ways. However, the authors note that this measurement technique has proved to be a valid predictor of the onset of bipolar disorder (Angst et al., 2003), and it also fits with the growing evidence base of experience sampling studies which show enhanced stress reactivity, perhaps encompassing mood instability, to be a mediator between adverse events and psychosis (e.g. Lataster et al., 2013).

3.5. Multi-factorial models

In order to advance our aetiological understanding of psychosis and inform future therapeutic priorities, the research highlighted above suggests the importance of assessing pathways from social adversity to psychosis. However, to our knowledge, there have been no published studies so far which have simultaneously assessed cognitive and affective pathways from adversity to clinically relevant first-episode psychosis, and which have provided empirical evidence that supports an entire, or even a substantial part of a cognitive model of psychosis. Nonetheless, research has begun to explore relationships between schemas, affective processes, and psychosis, and we can use this knowledge, as well as the theoretical hypotheses to begin to propose what the findings of a multi-factorial model might look like.

Research suggests that the concepts of negative schemas and affective processes are very likely to be interlinked, and depression and anxiety may arise from having negative schemas about the self (Garety & Freeman, 2013). Using a transdiagnostic sample of 115 patients with a combination of psychotic and affective diagnoses, Bentall et al. (2008) explored the relationship between self-esteem, affective processes and paranoia. They found that negative self-esteem completely mediated the relationship between dysphoria (measured by combining depression and anxiety scores) and paranoid beliefs. However, when dysphoria was included as a mediator between negative self-esteem and paranoia, no evidence of mediation was observed.

Further recent research using structural equation modelling also suggests that negative cognition (low self-esteem, self-critical thinking, and extreme negative beliefs about self and others) may play an important role in influencing paranoia (Fowler et al., 2012). Using a longitudinal study design, Fowler et al. (2012) examined a sample of 300 patients with psychosis with assessments at three time points over a one year period. Their main finding was that depressed mood and negative ideas about the self,

appeared to predict the strength of persecutory delusions over time, but interestingly, the researchers found no evidence for pathways in the opposite direction, i.e. that paranoia led to depression and negative cognition, which provides some tentative evidence that the concepts of depression and negative cognition may be causally related to the development of paranoia. Similarly to Bentall et al. (2008), Fowler et al. (2012) also found evidence for a pathway from depressed mood to paranoia that was mediated by negative schematic beliefs. Though, in this sample, it appeared that the final common pathway to paranoia was specifically via negative cognition as depressed mood had no independent association with paranoia in the presence of negative cognition. Despite some interesting findings and an admirable longitudinal design, the study is still correlational and therefore we still need to exert caution about the interpretation of the relationships, as well as be mindful of the possible effects of unmeasured variables. The authors note that in order to most accurately test their hypotheses, an experimental design would need to be employed (Fowler et al., 2012).

There have also been studies of general population samples which show affective processes to mediate the relationship between negative schemas and psychosis. Using a student sample of 700 adults, Oliver et al. (2012) assessed baseline levels (via the Internet) of negative schemas, current mood state over the past week, and delusional thinking to see whether negative schemas trigger delusional thinking through the mediating influence of negative mood. A subsample of 384 participants repeated the same measures six months later and it was found that baseline levels of negative schemas predicted higher rates of delusional thinking at time two. Indirect effect testing also revealed that the relationship between negative schemas and delusional thinking was partially mediated through anxiety. Interestingly, depression was not found to have a direct effect on delusions, and it also did not appear to mediate the relationship between negative schemas and delusional thoughts. This study is limited by a sample comprising 80% women which may bias the findings, as gender has been shown to be associated with reported levels of delusional distress (Freeman et al., 2005), as well as the use of web-based assessment which could influence further selection bias. However, the authors have made use of a large sample and a longitudinal dataset which spans both the UK and New Zealand.

Another clinical study by Ben-Zeev et al. (2009) also found that emotional dysfunction mediated the relationship between self-esteem and paranoia. A sample of 194 participants with a long-standing diagnosis of schizophrenia or schizoaffective disorder was assessed for their levels of self-esteem, symptoms of depression and

anxiety, and paranoia. The authors found a direct relationship between self-esteem and paranoia, with lower self-esteem associated with greater paranoia. The test of potential mediators revealed both depressive and anxiety symptoms mediated the relationship between self-esteem and symptoms of paranoia, although in contrast to the above study, the magnitude of the mediation effect was more substantial for depression than anxiety.

From the knowledge gleaned from theoretical propositions and empirical studies, we can begin to see how the pathways from adversity to psychosis via the mediating and moderating effects of negative schemas and affective processes might fit together. Evidence presented in the previous chapter suggests a direct pathway from adult adversity to psychosis, and evidence presented in this chapter suggests further direct pathways from negative schemas and affective symptoms to psychosis. From the limited amount of literature that has assessed the potential pathways of schemas and negative affect, we can tentatively assume that exposure to adult adversity increases the risk for psychosis through a pathway from adversity to psychosis via affective disturbances. As negative schemas are likely to be present prior to adult adversity, these are likely to act as a causal partner, whereby the effect of adult adversity combines with (or depends on) negative schemas to increase the risk of psychosis. Further evidence also suggests connections between all of the variables discussed: adversity, core schemas, affect and psychosis, with bidirectional relationships between schemas and affect described in the previous two paragraphs. Figure 2.2 displays the amalgamation of the findings presented in this chapter and the previous review chapter, and sets out a testable model with paths to be tested in this thesis. There also remains the possibility to explore the full model in future research.

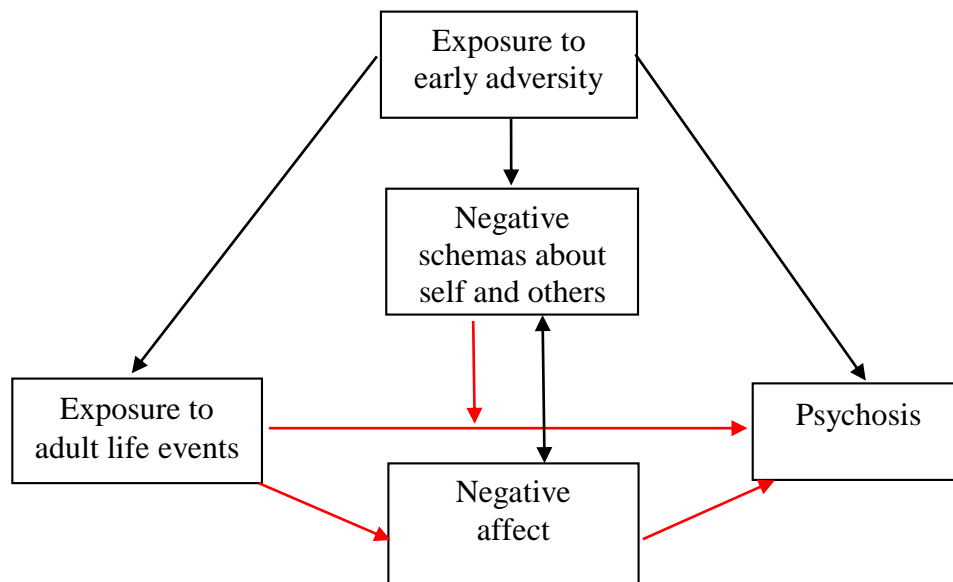


Figure 3.2 Putative relationships between adversity, schemas, negative affect and psychosis

→ indicates the paths to be tested in this thesis

3.6. Conclusions

An exploration of the literature has shown that there are several proposed cognitive and affective pathways that may lead to psychosis and which could also explain relationships between adversity and later disorder. Although there is an increasing literature which has investigated simple pathways from negative schemas to psychosis, or from affective processes to psychosis, there is limited research which has taken this a step further and begun to explore potential cognitive and affective pathways that may link exposure to stress and the later development of psychotic experiences. Importantly, no studies were found which have specifically assessed potential psychological pathways between recent adverse life events proximal to onset and clinically relevant psychosis. The research discussed in this chapter, and which has been drawn upon to inform this thesis, has come from studies of traumatic childhood exposures and perhaps more traumatic exposures in adulthood, akin to those which reach PTSD diagnostic criteria. Furthermore, the studies published to date which have explored these specific affective and psychological routes from social adversity to psychosis have all used general population samples that may not be generalisable to

those with clinical disorder, and therefore, it is not clear that these studies tell us anything about psychotic disorder. More research is clearly needed in order to gain a more thorough understanding of the potential and theoretically proposed pathways between adversity and psychosis. Assessment of these pathways in epidemiologically derived clinical samples that incorporate more detailed instruments of recent adversity is required to explore whether these proposed pathways exist after exposure to adverse adult life events close to the initial onset of psychotic symptoms.

In order to improve aetiological understanding and inform priorities for future interventions, it is important to gain a deeper understanding of these specific cognitive and affective pathways and the ways in which they interact with one another. Although deep-rooted negative schemas are notoriously difficult to change, psychological therapies that encourage individuals to take a more mindful and non-judgemental stance towards their schemas as they become activated may increase the likelihood that an alternative, and more helpful explanation is accepted (Oliver et al., 2012). Focusing efforts on enhancing positive schemas may also prove helpful as patients with higher positive self-schemas have been found to be more likely to achieve recovery (Chung et al., 2013). Furthermore, as research suggests that affective disturbances occur after exposure to adversity and these negative emotions are likely to predate the emergence of psychosis, interventions could focus on making use of evidence-based interventions for depression and anxiety in those at increased risk of psychotic disorder.

3.7. Summary of Chapter 3

Researchers have proposed a number of ways in which adversity may influence the later development of psychotic experiences. One possibility is a direct pathway from adversity to psychosis, whereby the experiences of hallucinations and delusions are apparent reactions to severe adversity, with overlapping content which mirrors previously distressing exposures. Empirical studies have shown this to be true for a small number of cases but it is questionable whether these individuals are experiencing a psychotic episode or rather symptoms of PTSD. It is clear that there are other pathways implicated in the stress-psychosis relationship.

Other indirect pathways are seen in the many contemporary cognitive models of psychosis. The cognitive model of Garety et al. (2001, 2007), which has informed the development of this thesis, suggests stressful experiences and psychosis are linked via a

combination of cognitive and affective processes. These processes include negative schemas about the self and others, and negative affect, including symptoms of depression and anxiety. It has been proposed that negative core schemas are formed early in life and are likely to be linked to adverse experiences in childhood. If an individual experiences further trauma later in life, these schemas become activated, leading to emotional changes which may not only cause the development of psychotic experiences, but alter the appraisal of these anomalous occurrences, further increasing distress, and preventing a benign explanation from being concluded.

Research supports the possibility of negative schemas as a mediator of the relationship between early trauma and psychosis, but no studies to date have tested the potential synergistic effects of schemas after exposure to further victimisation in adulthood. But theory suggests that exposure to severe adult life events could activate previously created negative schemas, which in turn increase the risk of psychosis. Research studies also support a pathway from adversity to psychosis via depression and anxiety. Within general population samples, anxiety has been shown to mediate the relationship between lifetime trauma and feelings of paranoia. When psychosis has been considered as a broader concept, both depression and anxiety appeared to mediate the relationship between severe childhood trauma and later psychotic experiences. Improved understanding of these pathways is imperative because it may enable psychological interventions to be better targeted at high-risk individuals to potentially prevent the emergence of psychosis.

CHAPTER 4 - Methodology

Synopsis

Data for this thesis were collected as part of a larger programme of research on first episode psychosis - the Wellcome Trust funded Childhood Adversity and Psychosis Study (CAPsy). This chapter will begin with a restatement of the main aims of this thesis, followed by a justification for the methodology (Section 4.1). This will be followed by a description of the general methodology for the larger CAPsy study, including more detail on its design, setting and recruitment protocol for cases and controls, as well as an outline of the study measures used for this thesis (Sections 4.2 and 4.3). The chapter will then elaborate further on the measures used to assess the role of life events and the potential psychological pathways (Sections 4.4 and 4.5). Finally, the chapter will end with a summary of the analysis plan (Section 4.6).

4.1. Aims and justification of study design

The main objectives of the work presented in this thesis are to explore associations between adult life events and difficulties and the onset of psychosis in an epidemiologically-derived case-control study, and to explore whether potential psychological pathways of negative schematic beliefs and affective processes are associated with increased odds of psychosis in those exposed to threatening events and difficulties. Cases are individuals with a first presentation of psychosis and controls are individuals with no current or past history of psychotic disorder drawn from the same population as cases.

The aims of this thesis are:

1. To compare the prevalence of adult life events and difficulties in cases and controls;
2. To compare the characteristics of the life events and difficulties reported by cases and controls, e.g. event and difficulty severity, type, intrusiveness, timing, focus, independence, and explore whether these factors are associated with an increased odds of psychosis;
3. To compare schematic beliefs and levels of depression and anxiety in cases and controls, and in controls with PLE;

4. Test theories of a cognitive model of psychosis to examine whether adult life events/difficulties and negative schematic beliefs combine synergistically to increase odds of psychosis, and whether the relationship between adult life events, difficulties and psychosis mediated by affective disturbances (i.e. depressive and anxiety symptoms);
5. Investigate whether the potential pathways between life events, cognitive/psychological disturbances and psychosis are also found within control participants who report sub-clinical psychotic experiences.

A first-presentation psychosis sample was selected to overcome some of the methodological limitations that are present in previous psychosis research. A first episode sample is optimum, for example, because it is not as subject to selection bias as a prevalence sample (which only includes those who have continued to be unwell and not died or migrated) and associations are not influenced by chronicity (as with a prevalence sample). In terms of the chosen design, some researchers view a prospective cohort design as the only way to identify causal relationships between risk factors and disorder; however, there are a variety of reasons why this is not suitable or feasible for psychotic disorder. The first reason for its lack of suitability is due to the fact that psychosis is a rare disorder with an approximate annual incidence rate of around 20 to 30 per 100,000 person risk years (McGrath et al., 2004) and an average age of onset of around 30 years (Kirkbride et al., 2006). Consequently, very large numbers would need to be initially recruited and followed over a large number of years to generate a large enough sample of individuals with a psychotic disorder. This is generally not feasible. To a degree, large population register data in Scandinavian countries provide relevant data on a sufficiently large number. However, there is an inevitable reliance on relatively crude routinely collected data in studies using these samples.

For all their shortcomings, case-control studies provide the best means to investigate, in detail, the impact of certain exposures. Given these considerations, as well as the enormous costs and time-consuming nature of conducting a longitudinal study, the incidence case-control design chosen for this thesis is justified. With this design, we have been able to assess many exposures in great detail, and also have the ability to explore a variety of potential confounders, mediators and moderators. Furthermore, a case-control design can be utilised to assess causality, as long as the study has been well designed and fulfils certain criteria (Susser et al., 2006). These steps

include minimising the likelihood of selection bias, trying to minimise the possibility of reverse causality by establishing the temporal order of exposure and disease, and taking steps to reduce information or misclassification bias. These issues have been carefully thought about in the design stage and have been addressed in a variety of ways, e.g. by employing an epidemiologically derived sample of incident cases and randomly selected controls, carefully dating the onset of psychosis and then ensuring the life events interview covers a period prior to this date, and taking account of event independence. These issues are addressed in more detail in the Discussion chapter (Chapter 8).

4.2. Methodology of the CAPsy Study

4.2.1. Background and design

This thesis draws upon data from the CAPsy study; an incidence and case-control study of first-episode psychosis which was designed to primarily investigate the relationship between childhood adversity and odds of psychosis onset, as well as exploring whether adversities in adulthood, and other psychological and/or biological processes modify the odds of disorder. Ethical approval for this study was agreed by the South London and Maudsley NHS Foundation Trust (SLaM) and the Institute of Psychiatry, Psychology & Neuroscience (IoPPN) Research Ethics Committee (Ref: 321/05, including amendments 1 to 9).

Cases and controls were recruited from two South East London boroughs – Lambeth and Southwark. According to 2011 Census data, the borough of Lambeth has a total population of 304,500 individuals; one of the highest populations in Inner London, and, with roughly 112 persons per hectare, it is also one of the most densely populated boroughs in London (Office for National Statistics [ONS], 2011). Lambeth is also notable for its ethnic diversity, with a particularly high proportion of black Caribbean (9.5%) and black African (11.6%) individuals (ONS, 2011). The borough is the 14th most deprived district in England, but, similar to other inner London boroughs, there are areas of affluence and deprivation often side by side (Department for Communities and Local Government, 2011). The borough of Southwark is recorded as having a total population of 288,700 individuals and is the ninth most densely populated of the 32 London boroughs, with a population density of approximately 100 persons per hectare (ONS, 2011). As with Lambeth, Southwark's population is ethnically diverse, with a

high proportion of black Caribbean (6.2%) and black African (16.4%) individuals, compared with both the national and London average (ONS, 2011). In terms of deprivation, the borough is ranked as the 41st most deprived district in England, which is a relative improvement from previous rankings (26th in 2007 and 17th in 2004) (Department for Communities and Local Government, 2011).

4.2.2. Sample selection and recruitment of psychosis cases

Adults who presented to SLaM inpatient and outpatient mental health services in Lambeth and Southwark (UK) for the first time with psychotic symptoms were included in the CAPsy case sample. Cases were considered eligible if they were experiencing either one positive psychotic symptom (for at least one day duration) or two negative psychotic symptoms (for at least six months duration), assessed using the Screening Schedule for Psychosis (Jablensky et al., 1992). A flow chart outlining the case recruitment process is shown in Figure 4.1.

Inclusion criteria were:

- a. Aged 18 to 64 years (inclusive);
- b. Resident within the catchment area, i.e. within either the London borough of Lambeth or Southwark, two of the four London boroughs served by SLaM. Residency was defined as: minimum of a one night stay at a residential address within Lambeth or Southwark, or detained in Brixton prison, irrespective of address pre-sentencing. Individuals who were homeless were discussed on a case by case basis;
- c. Had an untreated first presentation of a psychotic disorder (i.e. ICD diagnoses F20-29 and F30-33) (even if long-standing) during the study period (1st January 2010 to 1st January 2014);
- d. Were sufficiently fluent English speakers (i.e. did not require a translator).

Exclusion criteria were:

- a. Aged under 18 or over 64;
- b. Not resident within one of the study catchment areas;

- c. Evidence of prior contact with mental health services for an episode of psychosis outside of the study period;
- d. Evidence of psychotic symptoms precipitated by an organic cause;
- e. Transient psychotic symptoms resulting from an acute intoxication of alcohol or other psychoactive substance, as defined by ICD-10;
- f. Severe learning disabilities, defined by an IQ of less than 50 or a diagnosis of mental retardation;
- g. Not able to speak sufficient English to understand consent procedures and complete assessments.

In order to maximise recruitment rates and minimise selection bias, researchers used a thorough method to screen for potential cases. Case identification occurred through the weekly screening of both general adult inpatient and specialist psychosis inpatient services, as well as community mental health services, including early intervention services that specialise in treating patients with psychosis. The screening process involved researchers engaging in regular communication with doctors, nurses, care coordinators, and healthcare assistants to identify potential cases to approach, and also through the interrogation of case records to check for eligibility. Where possible, researchers would attend the weekly meetings of various community mental health teams and be present for the discussions of new referrals and ongoing caseloads. In many instances, eligible outpatients would first be approached by their care coordinators before being contacted by the research team. If researchers were in doubt over the eligibility of potential cases, they would interview the individual using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; WHO, 1994). Individuals would then be included if their symptoms scored at least a two (i.e. clinically relevant intensity and severity) on relevant items within the psychosis sections (i.e. Sections 17-20 within Part 2 of the SCAN interview).

A total of 885 patients were identified as being potentially eligible to take part in the study. However, we were not able to approach 328 individuals who were screened as eligible. Reasons for this included individuals being discharged from services, not attending appointments where the study could be introduced, and movement out of the catchment area. For those who could be approached (n=557), after agreement with their clinical team, a researcher would describe the specifics of the project and encourage them to ask any questions on aspects that needed further clarification. If the individual was willing and able to provide informed consent, the information sheet and consent

form would then be shared (see Appendix C). The individual was asked to carefully read through the consent form and confirm that they had understood the purpose and requirements of the project, as well as any risks involved. Due to the sensitive nature of some of the assessments, participants were assured that they could decline to answer any questions that they were not comfortable answering or drop out of the study at any time, without giving a reason. Signed consent forms were obtained from all of those who agreed to participate (n=328). Reasons for non-consent after approach included: individuals not being interested in the study; researchers unable to re-contact individuals after expression of interest; already taking part in another research study; being too busy; or had childcare responsibilities. After consent, 25 cases dropped out without completing any assessments. Reasons for drop-out included individuals refusing to take part after consent (n=12), being unable to be re-contacted (n=9), individuals who moved out of the area (n=2), or became ineligible (n=2) due to previous history of psychosis prior to January 2010.

Appointments were arranged with consented case participants in order to complete the assessments as soon as was feasible, and over as many sessions as were needed. The mean length of time between case participants' first contact with services and their first interview session for this study was calculated as a median length of 92 days and an inter-quartile range of 40-252 days. One of the reasons for this time lag was to ensure that cases were well enough to complete the study questionnaires as no interviews were conducted with patients who were floridly psychotic. Assessments were carried out by trained Research Workers, PhD students and psychiatrists. The battery was conducted either in an interview room on the psychiatric ward, at the community team base, at the IoPPN, or at the patient's home. The entire battery of assessments took on average 5 hours to complete and were completed across an average of three sessions. Participants were reimbursed up to £30 for their time and involvement in the study.

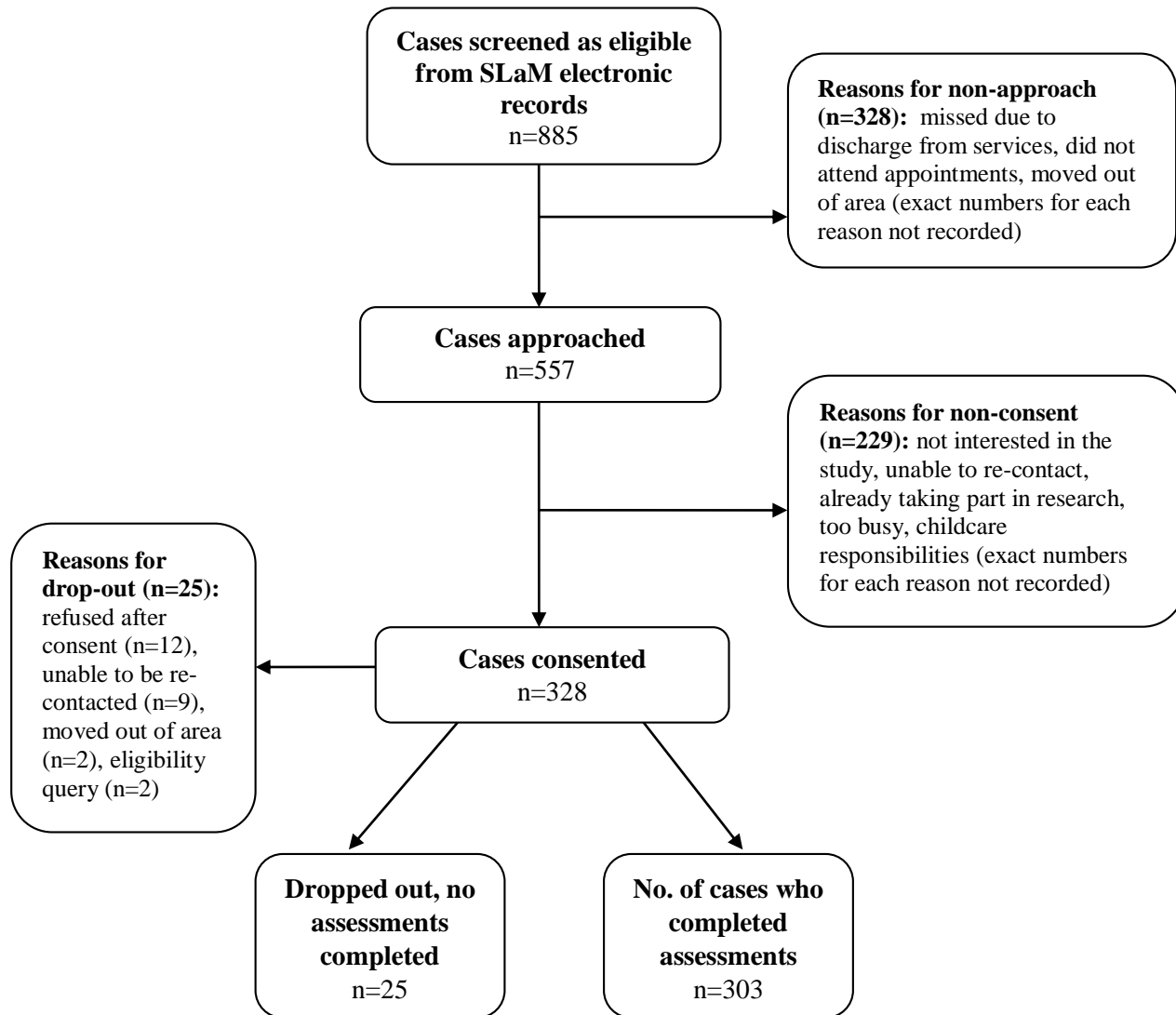


Figure 4.1 Flow chart for case recruitment

4.2.3. Recruitment of community controls

The inclusion and exclusion criteria for cases and controls were identical, with the exception that cases have psychosis. Potential controls were excluded if they had a current or past experience of a psychotic disorder.

General population controls were recruited from the same tightly defined catchment areas as cases, through the use of quota sampling and two key recruitment methods. The quota was based on 2011 census data and was used to ensure that the control sample was broadly representative of the local population in terms of age, gender and ethnicity. These quotas were then filled using the two methods described in the following section. Table 4.1 shows the initial quotas and the controls recruited by age, gender and ethnicity. For the wider study, black Caribbean and black African controls were oversampled to ensure a sufficient number for sub-analyses by ethnicity. Weights were generated to account for oversampling (i.e., to weight black Caribbean and black African controls back to their population proportions). These weights were consequently applied in all analyses to account for this oversampling using the survey options in Stata (or the `iweight` or `pweight` commands).

Once the quotas were in place, control participants were recruited using two main methods: 1) through sampling of GP surgeries and GP lists; and 2) via an ongoing community based study- the Biomedical Research Centre (BRC) South East London Community Health Survey (SELCoH) which recruited participants through the use of the Royal Mail Small Users Postal Address File (PAF; Jenkins & Meltzer, 1995) to randomly sample addresses within the catchment areas. Each of these recruitment methods will be described in more detail below. A flow chart detailing each stage of control recruitment is shown in Figure 4.2.

Firstly, all GP surgeries in the boroughs of Lambeth and Southwark were contacted with the help of the Primary Care Research Network (PCRN), and asked if they would be interested in assisting with the recruitment of participants for this study. Out of the 20 GP surgeries that replied to the PCRN, 12 were selected to help with the process of control recruitment. Of the eight GP surgeries that were not included in the control recruitment, six responded to say they were unable to help due to lack of time and resources. The PCRN decided not to include two further surgeries due to non-compliance in previous research studies. Over the course of control recruitment, 3600 individuals were randomly selected by the GP surgeries to take part in the study.

Practice managers filtered their GP lists to select individuals who met the study inclusion criteria. Invitation letters and an information pack for the study were sent to these individuals. Clinical codes were used to remove those with a known psychotic disorder. If no reply was received after two weeks, a follow-up letter was sent. Those who responded with interest were invited to come to the IoPPN for an assessment, or given the option to be seen at their home. It was anticipated that 5% of individuals would respond, resulting in approximately 20 positive responses, on average, from each surgery. Of the 3600 individuals who were invited to take part and did not consent to the study, the majority did not reply to the invitation letter (n=3085), others refused (n=287), and others were excluded for not meeting the eligibility criteria (n=55). A total of 168 (55.8%) control participants were consented via this method and went on to complete study assessments. A total of five individuals were excluded after consent for having a previous history of psychosis prior to January 2010 (n=3), for being over 65 years (n=1), and one control participant met inclusion criteria to be a case and was transferred across to the case arm.

Table 4.1. Quota and distribution of the recruited control sample for the CAPsy study

	Men n=147												Total
Age group	18-24 n=25				25-34 n=51				35+ n=71				
	W	BC	BA	Oth	W	BC	BA	Oth	W	BC	BA	Oth	
Quota	12	3	4	6	30	3	6	12	45	6	10	10	
Recruited	11	5	5	8	33	7	9	16	28	13	7	11	153
	Women n=143												
Age group	18-24 n=24				25-34 n=54				35+ n=65				
	W	BC	BA	Oth	W	BC	BA	Oth	W	BC	BA	Oth	
Quota	12	3	3	6	27	6	9	12	36	12	12	15	
Recruited	12	5	10	4	23	9	12	17	26	12	8	10	148

W, White British; BC, Black Caribbean; BA, Black African; O, Other (Other White, Asian, Other)

Secondly, additional controls were recruited from a follow-up of a community sample operating in the catchment area of Lambeth and Southwark; the SELCoH study (Hatch et al., 2011). From 2008 to 2010, the SELCoH team randomly identified private households in the boroughs of Lambeth and Southwark using the PAF, applying similar methods to the British National Psychiatric Morbidity surveys (Jenkins et al., 1997a/b). All addresses in Lambeth and Southwark were assigned a unique reference number and approximately 0.5% of all addresses (n=1110) were randomly selected to participate in the study using a random number generator. Around 60% of the selected addresses (n=695) were sent a letter describing the SELCoH study two weeks in advance of visiting. Interviewers then visited each selected household on at least four separate occasions at different times of the day (morning, afternoon and evening) and on different days of the week (including weekends), in an attempt to maximise the likelihood of a resident being at home and minimise sampling bias (e.g., more unemployed individuals are likely to be at home during the day). Residents were given written and verbal information concerning the study, and were asked whether anyone in the household might be eligible and interested in taking part. If all potential controls within the household refused, or no members were eligible, then the next address on the PAF list was visited. Reasons for non-consent via this method included no response to the invitation letter or home visits (n=369), refused to take part (n=96), and excluded due to not meeting the study eligibility criteria (n=95). Each member of the SELCoH sample who met our inclusion criteria was contacted by the CAPsy study and invited to the IoPPN for further assessments for our study. Of the final control sample, 133 participants (44.2%) were consented via this method. Two participants were excluded after consent for having a previous history of psychosis prior to January 2010.

Eligible controls who agreed to participate in the study provided written informed consent following a full explanation of the study and having read the information sheet (see Appendix C). Following consent, all potential control participants were screened for a history of psychosis with the Psychosis Screening Questionnaire (PSQ; Bebbington & Nayani, 1995). The PSQ comprises six questions covering symptoms of hypomania, thought insertion, paranoia, strange experiences and hallucinations, along with enquiry into past treatment for a psychiatric or psychological problem (see Appendix D). Those who reported current or previous treatment for psychosis were automatically excluded (n=4), but those who had received treatment for other disorders without any psychotic features (e.g. depression) were able to proceed

with the assessment battery. Any control participants who were suspected of currently experiencing an undisclosed psychotic disorder were further interviewed with the psychosis section of the SCAN (WHO, 1994), and were considered for inclusion as a case participant if a psychotic disorder was confirmed by the SCAN interview. After further probing and team discussion, one control participant was transferred to the case arm. Controls that gave positive responses on the PSQ but did not meet criteria for a psychotic disorder remained within the control group. Controls were assessed with an identical battery to the patients with the exception of the clinical interview schedules.

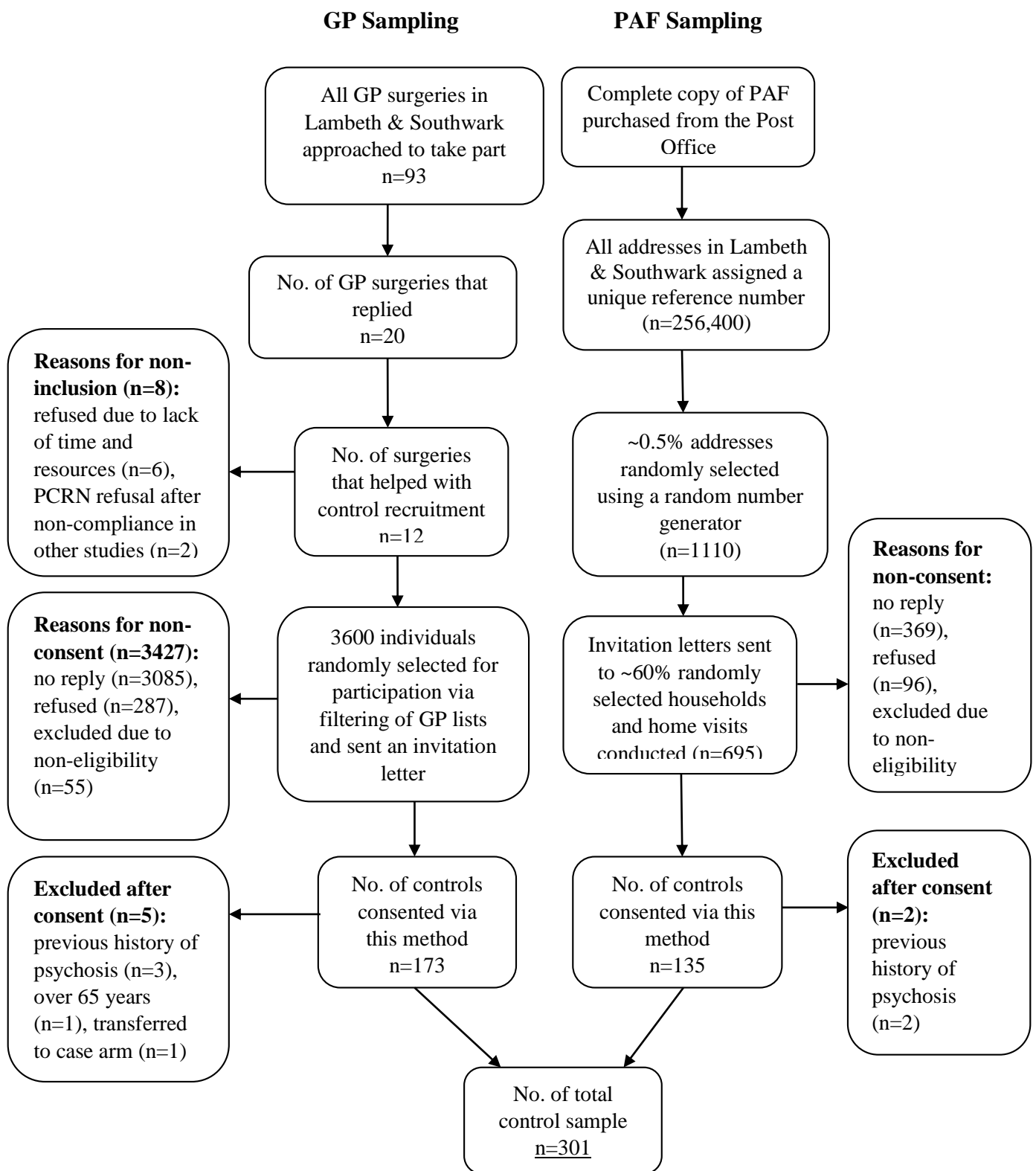


Figure 4.2 Flow chart for control recruitment

CAPsy= Childhood Adversity and Psychosis study; GP= General Practice PAF= Postal Address File; PCRN= Primary Care Research Network; SELCoH= South East London Community Health Survey

4.3. Main assessment tools

An extensive battery of assessments was conducted for the CAPsy study. The measures included diagnostic instruments, psychosocial questionnaires, neuropsychological testing and biological measurements. Only the relevant measures used in the analysis of this thesis are outlined below.

Medical Research Council (MRC) Sociodemographic Schedule (Mallet, 1997)

An amended version of the MRC Sociodemographic Schedule was completed by all case and control participants. The questionnaire aims to collect data on current and past social circumstances, including individual and parental place of birth, migration history, and current and past addresses. The variables that are relevant for the analyses of this thesis are the participants' date of birth, their gender, ethnicity, education level, employment status, relationship status and living arrangements, and participant and parental social class. Gender was classified as male or female and age at interview was split into 18-29 and 30-64 years for the analysis.

Participants were asked about their ethnicity and to describe their ethnic origin according to the 18 categories employed by the 2011 UK Office of National Statistics census. If this question was not completed for the case participants, the clinical case notes and/or medical staff were consulted, and their suggestion was noted. Where ethnicity was ambiguous, the available information was discussed by the local study team (including at least one expert in ethnicity and mental health), and a consensus decision was reached. The 18 categories were transformed for the analysis by collapsing the smallest ethnicity categories into an 'Other' group (Mixed groups, Black Other and Other), a 'White Other' group (White Irish, White Gypsy and White Other), and an 'Asian (all)' group (Indian, Pakistani, Bangladeshi, Chinese and Other Asian). This left six main ethnic groups in total: White British, White Other, Black Caribbean, Black African, Asian (all) and Other.

The participants were also asked about the highest level of education that they had achieved. This was recoded into three categories for the analysis from the original six-category variable and was comprised of: 'School – left with no qualifications or with qualifications', by combining the two original categories of school, no qualifications (to end of compulsory education; passed no exams, tests, etc.) and school, with qualifications (to end of compulsory education; passed one or more exams, tests,

etc.); ‘Further Education’, by combining the two original categories of tertiary/further (first level of non-compulsory education; e.g. A-levels, Baccalaureate) and vocational (job related education, e.g. teacher training, plumber, electrician, etc.); and ‘Higher Education’, by combining the two original categories of higher (undergraduate) (university; first degree) and higher (postgraduate) (university: higher than first degree level, e.g. Masters, PhD).

Information on employment status was available for different time periods: current employment status at the time of the interview, at the time of onset (for cases only), one year prior to onset (cases) or to interview (controls), and five years prior to onset (cases) or interview (controls). If participants were aged less than 17 years during the time period in question, their answers were coded as ‘not applicable’. For the analyses, employment status was collapsed into four groups from an original six-category variable: ‘Employed’, by combining the three original categories of part-time employee, full-time employee and self-employed; ‘Student’; ‘Unemployed’ and ‘Economically Inactive’ (i.e. house person, physical illness/disability, carer, retired).

Data on relationship status and living arrangements was also collected according to the four time periods described above. As before, a rating of ‘not applicable’ was given for any participants who were aged less than 17 years at the time of each rating period. For relationship status, the original five categories were collapsed into a binary variable which was comprised of - ‘Single’, by combining the original three categories of single, divorced/separated, widowed; and ‘In a relationship’, by combining the original two categories of married/living with someone and in a steady relationship. For living arrangements, these variables were also recoded to form a new binary outcome variable, either living ‘Alone’, comprising the two original categories of alone and alone with children; and ‘With others’, which comprised the remaining six original categories of partner/spouse, partner/spouse and children, parents, other family, friends, other (e.g. hostel, halls of residence).

Subject social class was rated for each participant for two time points- main and current. Parental social class concerned the main breadwinner of the family, and was also rated for two time points- at participant’s birth and their main occupation during the participant’s childhood, using the European Socio-Economic Classification system (ESeC). The ESeC contains ten classes in which to rate social class. These are as follows: (1) Large employers, higher grade professional, administrative and managerial occupations; (2) Lower grade professional, administrative and managerial occupations

and higher grade technician and supervisory occupations; (3) Intermediate occupations; (4) Small employer and self-employed occupations (excluding agriculture); (5) Self-employed occupations; (6) Lower supervisory and lower technician occupations; (7) Lower services, sales and clerical occupations; (8) Lower technical occupations; (9) Routine occupations; (10) Never worked and long-term unemployed (six months or more). Additional codes were used for full-time students (11), and non-classifiable (12), which included the economically inactive, e.g. carers, housewives, retirees, and any unknown occupation or occupations that did not fit into any of the previous categories. For the purposes of this thesis, the categories were collapsed into a six-class model, as follows: ‘Salaried’ (1 & 2), ‘Intermediate’ (3, 4, 5, 6), ‘Working Class’ (7, 8, 9), ‘Never Worked/Long-Term Unemployed’ (10), ‘Student’ (11), and ‘Non-classifiable’ (12).

Nottingham Onset Schedule (NOS-DUP; Singh et al., 2005)

The NOS-DUP was used to determine the date of onset of psychotic symptoms in the case subjects in advance of completing the LEDS interview. The calculation was made by collating information from the participant, clinical notes, and/or clinical teams. Onset was defined as clear evidence of positive psychotic symptomatology, i.e. delusions, hallucinations in any modality, first-rank symptoms, or catatonia, as measured by a score of at least two for a psychotic item in Part II of the SCAN (WHO, 1994). The duration of untreated psychosis (DUP) was defined as the time period in days between onset of the first psychotic symptom and the first contact with secondary mental health services.

Psychosis Screening Questionnaire (PSQ; Bebbington & Nayani, 1995)

The PSQ was used to assess the presence of psychotic symptoms within the control sample. The PSQ is a structured clinical questionnaire which assesses psychotic experiences within the last year across five domains: hypomania, thought disorder, paranoia, strange experiences and hallucinations (see Appendix D). It is structured so that each of the five domains contain an initial probe question and one or two follow-up ‘key’ questions, which are only asked if the initial probe question is endorsed. These key questions help to distinguish experiences that are likely to be common and part of normal experience, from those which are perhaps more unusual and may be clinically relevant. For control participants to be included in the subclinical psychosis group

within this thesis, they must have answered ‘yes’ to all questions within each symptom category, except for the paranoia category, where subjects only needed to have answered ‘yes’ to the first follow-up question, rather than the second question as well. The second paranoia key question relates specifically to delusions of conspiracy, and therefore using this probe to derive potential cases may exclude other forms of paranoid delusion. Researchers have also adapted the method to exclude the hypomania category and focus solely on the positive psychotic symptoms (Wiles et al., 2006), or presented findings from PSQ analyses with and without the addition of the hypomania questions (Morgan et al., 2009). Justifications for excluding the hypomania category include its potential lack of specificity for psychosis compared to the other four categories, and its questionable response rates which have often been reported to be greatly in excess of the other items (e.g. Murphy et al., 2014). Participants with PLE in this study were identified using these methods described and results were reported with and without the addition of the hypomania category.

Split Global Assessment of Functioning scale (S-GAF; Pedersen et al., 2007)

The GAF is based on the widely used Global Assessment Scale (Endicott et al., 1976) and was first included as axis V in the revised third edition of the Diagnostic and Statistical Manual (DSM-III-R; American Psychiatric Association, 1987). The original scale provided a single rating scale for evaluating an individual’s psychological, social and occupational functioning on a hypothetical continuum of mental health. Scores range from 1-100, with 1 representing, hypothetically, the most unwell, to 100, representing the hypothetically healthiest. The scale is divided into ten equal parts and gives descriptions of defining characteristics, including information on symptoms and social functioning, for each 10-point interval.

A modified version of the original scale, known as the S-GAF, was used for the CAPsy study by splitting the global functioning score into two to give a separate score for symptoms and a separate score for functioning (Pedersen et al., 2007). Both variables were scored from 1-100 and were rated for each participant according to their symptomatology and functioning over the past month prior to interview.

Family Interview for Genetic Studies (FIGS; NIMH Genetics Initiative, 1992)

The FIGS measure was used to collect information about the participant's family history of mental illness and was included as an indirect measure of genetic risk. The interview is conducted by firstly constructing a pedigree diagram for the participant's first degree family members, and then administering a series of screening questionnaires to elicit details about possible mental health problems in these relatives. The questions enquired about possible depression, mania, psychosis, obsessive compulsive disorder, and autism. If any screening questions were answered positively, follow-up questions to elicit symptom and treatment information were asked in relation to each potentially affected relative. Both family history of any mental disorder in first-degree relatives, i.e. biological parents, siblings and children, and family history of psychosis, were included in the analysis.

Cannabis Experience Questionnaire (Modified version; Di Forti et al., 2009)

This questionnaire was developed from the original Cannabis Experiences Questionnaire (CEQ; Barkus et al., 2006) which was designed to measure psychological experiences whilst under the influence of cannabis. The modified version was expanded to collect further information on current and/or past cannabis use, such as age at first use, and the frequency and type of cannabis used. For the analyses of this thesis, information on current cannabis use was utilised, defined as at least a single use of cannabis in the last year, and also any lifetime use.

4.4. Primary Exposure - *Life Events and Difficulties Schedule (LEDS; Brown & Harris, 1989a) (Appendix E)*

Information on adult life events and difficulties was obtained using the Life Events and Difficulties Schedule (LEDS; Brown & Harris, 1989a). The LEDS is a semi-structured interview measure that elicits information concerning events and difficulties that have occurred during a predetermined period prior to illness onset or interview. For this study, the LEDS was administered as a face-to-face interview and the time-frame chosen was the year preceding the date of onset of psychosis as defined by the NOS-DUP (cases) or the date of interview (controls). The aim of the LEDS interview is to gather a substantial amount of information in order to be able to rate events and difficulties contextually within a consensus meeting. This particular measure of life

events was chosen over a cruder checklist measure as it allows for the impact of events and difficulties to be more fully characterised by taking account of various characteristics of the experiences, such as severity, duration and independence from hypothetical disorder.

4.4.1. Development of the measure

The LEDS is a semi-structured interview measure used to elicit, record, and date the occurrence of life events and difficulties. It is considered to be the gold-standard instrument to assess life events (Brown & Harris, 1989b). The schedule emerged, in part, as a result of the authors' dissatisfaction with the commonly used checklist approach and its ineffectiveness in elucidating the stress-illness link (Brown & Harris, 1989b). The first step in creating the measure was to decide what events would actually be classed as a life event, as opposed to less severe 'incidents', and then to draw up a list of equivalent classes of events across multiple domains, all with extensive examples to support their severity rating. The authors note that one of the key considerations of deciding what would be classed as a life event, based on their research on patients with schizophrenia (Brown & Birley, 1968), was to define an event in terms of its likelihood to produce a strong emotional reaction of any kind (Brown & Harris, 1989b). It was agreed that events were largely restricted to those involving the subject and their close ties, i.e. their partner, children, parents, siblings, close friends or cohabiters, but severe events involving more distant relatives or even strangers could be included, providing the subject was present at the time of the event.

The authors found that the 40 original event types categorised for the development of the LEDS measure could be condensed into eight groups, with every event involving a change in activity, role, person, or idea (Brown & Harris, 1989b). The eight groups are: changes in role for the subject, e.g. a new job, or starting a new relationship; major changes in role for the subject's close tie(s) or member of the household; major changes in the subject's health; major changes in the health of close ties or household members; residence changes or marked changes in the amount of contact with close ties or household members; forecasts of change, e.g. being told about redundancy; fulfilments or disappointments of a valued goal; other dramatic events involving the subject or a close tie (Brown & Harris, 1989b).

The LEDS-2 manual (Brown & Harris, 1989a) provides examples for a myriad of different event possibilities, with detailed instructions to guide the interviewer on which events should be included, as well as guidance on their severity ratings. As outlined in the paragraph above, an event must involve a change of some kind, and therefore the threshold for what will be counted as an event to be later rated is sufficiently high. Consequently, many incidents reported by participants during the course of a LEDS interview are often excluded from the eventual ratings.

The Brown and Harris (1978, 1989a) method extends the investigation of life events to also include more chronic difficulties. A consideration of difficulties was added to the LEDS approach as the authors appreciated that discrete life events may not be the only form of adversity indicated in stress research (Brown & Harris, 1989b). Difficulties are defined as problematic situations that last for a minimum of four weeks. They can coexist in time with events and therefore the details of relevant events are considered within the difficulty rating. As with events, a similar manual has been devised for rating difficulties which covers several thousand examples (Brown & Harris, 1979).

4.4.2. Psychometric properties

Since its creation, the LEDS interview has demonstrated robust reliability and validity (Brown & Harris, 1989b). One way researchers have tested its level of accuracy and agreement is to compare the independent reports of two informants, i.e. information from the participant, with information from a close tie. Research has demonstrated 81% agreement between patients with schizophrenia and their relatives for the reporting of the patients' recent life event history in the three months before onset (Brown et al., 1973), which demonstrates concurrent validity. Research has also demonstrated this level of agreement across a 12 month period, which is the time period considered for this thesis (Brown et al., 1973). Using a sample of patients with depression, Brown et al. (1973) found a 78% agreement between relatives and patients on whether an event had occurred. Interestingly, this agreement rose even further to 91% for events of at least moderate severity. As well as testing the agreement of an event occurrence, researchers have also assessed relative-patient reliability with regard to the dating of events. In their sample of patients with depression, Brown and Harris (1982) report that the average difference in the dating of an event by both respondents was only 2.4 weeks, and the

vast majority (79% of pairs), did not differ in their dating of events by more than 3 weeks and 90% did not differ by more than 5 weeks.

In terms of its reliability, the LEDS approach has been shown to have good inter-rater reliability. The level of agreement on long-term contextual threat ratings between the original raters in the Brown and Birley (1968) schizophrenia study was 0.75 (reported in Brown et al., 1973), and disagreement between raters on the various scales was stated to be uncommon (Brown & Birley, 1968). Inter-rater reliability has also been shown across longer periods of life events assessment. In the Bebbington et al. (1993) study, which considered the experiences of patients six months prior to onset of psychosis, the agreement levels were found to be high, with 81% agreement on the level of long-term contextual threat. Although no studies have considered the inter-rater reliability for LEDS interviews covering the one year period before psychosis onset, high inter-rater reliability has been found over a year-long period in patients with depression and in unaffected control subjects (Brown & Harris, 1989b). The reliability of other LEDS dimensions over a 12-month period has also been found to be high both in unaffected controls and patients with depression, with at least 90% agreement between raters on most measures (Brown & Harris, 1989b). Taken together, the evidence is that the LEDS is reliable if formal training is undertaken, although inter-rater reliability has been shown to be acceptable even after administration of brief training (Tennant et al., 1979). Overall, these findings suggest that the LEDS measure is appropriate and reliable for use with a sample of patients with psychosis and that external confirmation of events is not essential.

Within the CAPsy study, measures were put in place to minimise the likelihood of investigator bias and improve reliability. Firstly, all researchers who administered the LEDS interview were given an intensive week-long training session at the beginning of the study period, in order to acquire the expertise needed to administer the interview and rate its many characteristics. Throughout the duration of the study, regular ‘top-up’ training was provided to ensure researchers continued to rate accurately and consistently. All of the LEDS ratings were made by at least three researchers during weekly consensus meetings, which were attended by all CAPsy researchers who conducted the LEDS interview. Researchers ensured they adhered to the strict coding guidelines as set out in the manual and would consult it for any challenging ratings.

Every LEDS rating was then further checked by myself and at least one other member of the team at the end of the study in order to check for consistency and amend

any errors within the ratings. As the researchers were not blinded and were aware of case-control status during the interview and rating process, these steps were considered necessary to minimise the impact of investigator bias, and increase inter-rater reliability.

4.4.3. Composition and scoring procedures

Life events and difficulties elicited by a modified LEDS-2 measure (Brown & Harris, 1989a) used in this thesis were rated on the following scales:

1. Start date (and end date for difficulties)
2. Duration of chronic difficulties (in months, from 1-12 months)
3. Type classification (e.g. education, work, health, etc.)
4. Focus (e.g. subject, other, etc.)
5. Independence (from hypothetical disorder)
6. Contextual threat (short-term and long-term)
7. Intrusiveness

Dating of events and difficulties/duration of difficulties

All events and difficulties were rated for their start date, which was sought during the course of the LEDS interview. Only difficulties were given an end date, which can be dated as the last date of the interview period for difficulties that are ongoing. The duration of the difficulty (in months from 1-12 months), was also noted. Where dating was not immediately clear, an attempt to anchor dates in relation to public holidays and birthdays was often helpful. Where there was still doubt over the dating of events and difficulties, a doubt rating was recorded, and the midpoint of the month (15th) was taken (Brown et al., 1973).

For the analyses, events were grouped according to whether they fell in the 1st, 2nd, 3rd or 4th quarter of the year in which they occurred and these time periods were compared to see whether there were more events occurring in different quarters between cases and controls, e.g. for cases, whether events cluster closer to onset and occur more frequently in the final quarter, compared with control subjects.

The duration of difficulties was also compared between cases and controls to see whether length of difficulties was affected by case status. Difficulty duration was recoded to form two levels: difficulties lasting between 1-6 months, or 7-12 months.

Type classification

All events and difficulties were classified according to their type in one of eleven domains. These were education (0), work (1), reproduction (2), housing (3), money/possessions (4), crime/legal (5), health/treatment/accidents (6), marital and partner relationships (7), other relationships (8), miscellaneous (9), and death (10). Although this scale is fairly self-explanatory, there were instances where the event or difficulty crossed multiple domains, e.g. if a husband commits a crime, deciding whether this would rate under the marital/partner category or under crime. In order to come to a consensus about this decision, the LEDS-2 manual (Brown & Harris, 1989a), outlines a number of rules to help guide researchers on which domain is deemed the most appropriate. These rules are set out in detail under the relevant sections for each of the ten domains. If researchers were unsure of the type classification, they would firstly refer to the manual and then consult either George Brown or Tirril Harris directly if further clarification was needed.

Focus

The focus rating identifies whether the subject or another person was mainly involved in the event or difficulty. Focus was given a rating of 1-4, with events and difficulties focused solely on the subject given a rating of '1-subject-focused', e.g. subject started a new job; events and difficulties containing shared involvement with another person, e.g. start of a romantic relationship, were rated as a '2-joint-focused'; events where the subject's possessions were involved, such as a burglary where relatively little of value was lost, or a burst pipe caused damage to the house but no residential relocation was required, were rated as '3-subject's possession'; and lastly, events and difficulties concerning another person, e.g. spouse began a new job, were given a focus rating of '4-other person'.

According to Brown and Harris (1989a), the focus scale is a critical element of the LEDS measure because only events rated as '2-moderate' or '1-marked' on long-term threat, and which were also focussed on the subject (either solely or jointly) have been

associated with onset in research on depression. It seems plausible that this would also be true for psychosis.

For the analyses, the foci of events and difficulties were recoded to compare a new group of 'subject focussed' events and difficulties which included focus ratings of 1 (solely subject focused), and these were compared to another condensed group of 'joint and other focused' events and difficulties, which included focus ratings of 2, 3 or 4.

Independence

A significant proportion of previous research assessing the impact of life events on illness is limited by the lack of consideration that an event may occur due to the insidious development of the disorder in question, or alternatively that the measurement of the event could be influenced by the subject's attempt to find an explanation for their disorder, so called 'effort after meaning' bias (Brown & Harris, 1989b; Beards et al., 2013). In both of these instances, it is possible that these pre-onset events are not totally 'independent' from the outcome being assessed. As a result of these considerations, Brown and Harris (1978), an 'independence' scale to distinguish events which are unlikely to be the result of the disorder under study because their source was clearly 'independent' of the subject's agency (and therefore necessarily of any hypothetical developing symptomatology). Events are deemed to be 'independent' because the origins of the event are essentially external to the subject and there is not too much likelihood of an insidious disorder having brought about the event. Examples of 'independent' events include the death of a family member or a natural disaster. Events which cannot clearly be rated 'independent' are termed 'possibly independent', and these include events where the individual's personality and potential emerging symptoms could have influenced its occurrence. The majority of occurrences are deemed as 'possibly independent' and examples include being fired from a job and relationship problems. In their LEDS-2 manual, Brown and Harris (1989a) add that when rating independence, it is not necessary to know the subject's psychiatric state, and, suggest that the independence rating is made as though this was unknown (Brown & Harris, 1989a).

Threat

In order to address the issue of subjective interpretation, Brown (1981) introduced a 'contextual threat' rating, and all events and difficulties are rated for their severity based on how a person of a similar biography to the participant in question would respond. This thesis considers contextual threat, using the investigator's assessment of likely threat based on relevant background information. For example, when making a contextual threat rating of a birth, it is necessary for the rater to know about the relevant context, including the number of children the subject already has, the financial and housing situation, quality of the relationship with their partner, whether the pregnancy was planned and what life-changes are involved. The level of threat ratings should be rated with reference to the precedents set out in the LEDS-2 manual (Brown & Harris, 1989a). However, the authors do note that the rules and examples are for general guidance only. It is always possible for the rater to break from an 'anchoring example' rating if a case can be made for the presence of contextual factors that either increase or decrease the 'standard' ratings.

Threat is rated by the researchers according to the overall 'unpleasantness', i.e. the ongoing negative feelings associated with the event or difficulty, and the uncertainty and anticipation of difficulty surrounding the consequence, i.e. the 'threat'. Brown and Harris (1989b) note that many events and difficulties are likely to be both unpleasant and threatening, and that these two aspects which encompass the overall threat rating are not directly distinguished in the threat scales themselves.

Event threat was given two ratings, events were firstly rated for their short-term, or immediate impact, i.e. for the first few days after the event, and also for their longer term impact, roughly 10-14 days after the event occurred. The long-term threat rating deals particularly with the threatening aspects of the event, although unpleasantness is taken into account. Events were rated using a four-point scale of '1-Marked threat/unpleasantness'; '2-Moderate threat/unpleasantness'; '3-Some threat/unpleasantness'; '4-Little or no threat/unpleasantness'.

Events rated as 'marked' on long-term threat were reserved for events where the threat to the subject was expected to be considerable. Examples include the death of spouse or other close relative, life-threatening illness to subject or spouse, and the subject giving birth to a severely handicapped baby. The 'moderate' long-term threat category was used for the majority of unpleasant or threatening events. Events rated as either marked or moderate on long-term threat have been found to cover most of the

events that are associated with depressive disorder (Brown & Harris, 1989b). Examples of moderate events given in the manual include the loss of a close confidant who leaves the area and had previously been seen daily by the subject, and the illness of a partner with bronchitis who was admitted to hospital for one week and likely to need considerable time off work (Brown & Harris, 1989a). A rating of 'some' on long-term threat was given to events which still contained some threat or unpleasantness, but they did not have the seriousness of the 'moderate' rating in terms of implications. A disturbing, unpleasant and threatening situation may well have greatly improved in the short term leaving only 'some' long-term threat rating a fortnight after the event took place, e.g. being attacked in a local street with no long-term physical problems, and no robbery. A rating of 'little/no threat' was given for long-term threat if the negative implications of an event had cleared up totally by the end of the second week after the event. This included events which were essentially positive in nature, such as starting a new relationship with an 'acceptable person', moving to a better house, moving to an apparently 'better' job. This category also included routine or 'milestone' events, e.g. child starts school, unless it involves unusual problems.

Difficulties were rated along a similar dimension of threat/unpleasantness; but the concept of a difficulty, unlike that of an event, already has the notion of some type of negative attribute built into it. The threat scale for difficulties is more elaborate than the scale for events by containing seven, rather than four points, but the standards correspond fairly closely between the two scales. Difficulties were rated as: '1-High marked'; '2-Low marked'; '3-High moderate'; '4-Low moderate'; '5-Mild'; '6-Very mild'; or '7-Not/no longer a difficulty', and were rated for their long-term threat only.

For the majority of the analyses in this thesis, as with other event studies, only the long-term threat rating was used (e.g. Bebbington et al., 1993; Raune et al., 2009). The contextual threat ratings are considered to be critical for aetiological research (Brown & Harris, 1989b), and the long-term rating has been given more weight due to the nature of many events being self-limiting, and resolving once the immediate consequences are over (i.e. leading to a lowering in the long-term threat rating). There are some events which are not self-limiting and they hold obvious implications for the longer-term situation even when the event itself is over (e.g. birth of a baby; a proposal of marriage; partner receiving a diagnosis of cancer).

In the analyses, event threat was regrouped to form a new dichotomous variable, by combining the events rated as marked or moderate for long-term threat, 'severe

events', and comparing these to 'no/non-severe events', created by combining exposure to no events, and to events rated as some or little/none on both short and long-term threat, or rated as marked or moderate for short-term threat only. A similar dichotomy was also used for the analysis of difficulties by grouping together the marked and high moderate ratings, i.e. high marked, low marked, high moderate to form a new 'severe difficulties' category, and comparing these to either no difficulties or difficulties rated as low moderate, mild/very mild and not/no longer a difficulty categories, which were grouped together to form a new 'no/non-severe difficulties' category.

Intrusiveness

An additional scale was used to classify events and difficulties by measuring the degree of intrusiveness. Intrusiveness is the degree of interference and/or attempted control of the participant by others. This is usually from outsiders or people where there is no evidence of closeness, but a special case can be made for including people who are not outsiders to the participant, e.g. if a subject was raped by their partner. Furthermore, usually, but not always, intrusive events involve intent to harm and will often be committed by a figure of authority. Intrusiveness was rated on a four-point scale: '1-Marked intrusiveness'; '2-Moderate intrusiveness'; '3-Some intrusiveness'; '4-Little or no intrusiveness'. All events and difficulties were rated on their intrusiveness irrespective of their threat level.

For the analyses, events with any intrusion were grouped together, i.e. events rated as having marked, moderate, or some intrusion, were combined to form an 'intrusive events' category, and were compared to those events rated as having little or no intrusiveness, which formed a 'non-intrusive events' category. The same cut points were used to separate intrusive difficulties from non-intrusive difficulties.

4.4.4. Administration of the LEDS interview

The LEDS interview was conducted during the beginning stages of the comprehensive CAPsy study battery and was usually the second assessment to be administered after the MRC Sociodemographic Schedule. If case participants were actively psychotic and it was not appropriate to conduct the interview, then this was administered later in the assessment battery. Furthermore, if researchers were concerned

that the case did not provide reliable information, then the information given would also be corroborated at a later appointment.

The interviewer began the LEDS interview by asking about each event type in turn, starting with health events. Prior to this, the interviewer would firstly clarify the date of illness onset for case subjects using the NOS-DUP, and then clearly explain that the current interview would relate to the year prior to this for cases, and the one year prior to the interview date for control participants. In most instances, the interviewer would draw out a timeline to aid this process and where the interviewer had any concerns about memory, these were noted on the interview schedule and were taken into consideration when rating; i.e. more conservative estimates would be given in these instances, or information would be left as missing. Participants would also be asked about their main confidants and close ties and the interviewer would reiterate that the questions concern the subject themselves and the aforementioned close ties. During the interview, if the subject responded positively to one of the probe questions, the interviewer would then ask further questions about the event or difficulty in order to help rate the contextual elements. The interviewer would ask about the situations which led to the event occurring, what followed afterwards, and the full set of circumstances surrounding its occurrence. The interview would end once the full list of topics and subsequent probes had been discussed and the interviewer was satisfied that enough information had been gathered to rate each aspect of the events and difficulties discussed.

In any situations where the interview had brought back painful memories and the participant became noticeably distressed, the researcher would clarify whether the participant would like to continue, and if not, the interview would be terminated, and if appropriate, recommenced at a later session. If participants were particularly upset, researchers would advise them to contact their care coordinator or GP for advice, or the interviewer would contact the clinical team where there were concerns for a case subject's welfare.

4.4.5. Ratings Procedure

After the history of events and difficulties was elicited, ratings were then made according to the technique developed by Brown and Harris (1978). For purposes of reliability, the early event ratings were made following extensive training, and all

unusual or idiosyncratic events were presented to other researchers trained in the method at weekly ‘consensus’ meetings at the IoPPN. Prior to and during these meetings, the LEDS-2 manual (Brown & Harris, 1989a), was consulted extensively in order to maintain consistency and adherence to their substantial collection of example LEDS ratings.

A typical consensus meeting involved three or more members of the team experienced in the use of the LEDS measure. The person who conducted the interview would introduce the subject whose events and difficulties were to be rated with the necessary amount of background demographic information (such as age, sex, marital status, occupation, number of children). The interviewer then read out the details of each event and difficulty, dealing with them in chronological order, one at a time. Events were rated in temporal order, without any consideration of eventual outcome (i.e. after the long-term period of 10-14 days). The team members would typically ask for further information about each event and what they considered to be relevant contextual material. The ratings were then made individually, and an agreement was reached. This was often done without discussion by following the majority rating. However, occasionally a longer discussion followed if individual ratings were considerably different.

4.5. Measures of Psychological Mechanisms

Information relating to the potential psychological pathways between life events, difficulties and psychosis was elicited using the following three questionnaires:

4.5.1. Brief Core Schema Scales (BCSS; Fowler et al, 2006b)

The BCSS was used to measure the participants’ self-report of schemata concerning the self and others and contains 24 items that are assessed on a five-point rating scale (0-4). A copy of the measure is provided in Appendix F. Four scores were obtained: negative-self (six items), positive-self (six items), negative-others (six items), and positive-others (six items), each with a total score of 0-24. The participant was asked to indicate in a dichotomous No/Yes format whether they held each belief, and if they answered positively, to indicate their degree of belief conviction by circling a number from 1 to 4 (believe it slightly, believe it moderately, believe it very much, or

believe it totally). The content of the negative-self subscale was derived from self-devaluative words used by Teasdale and Dent (1987) and subsequently by Teasdale and Cox (2001) as globally negative self-descriptors of personality. The other items were generated by David Fowler and Daniel Freeman on the basis of clinical experience with paranoia (Fowler et al., 2006b). The measure is very brief, and takes an average of 1 minute 25 seconds (SD = 4 seconds) to complete (Fowler et al., 2006b).

Psychometric properties

The BCSS has been reported to have good psychometric properties over a variety of constructs (Fowler et al., 2006b). The internal consistency of all four schema subscales has been reported as high for both non-clinical and clinical samples. For the clinical samples, the following Cronbach's alpha coefficients have been reported: positive self-schema- 0.79, negative self-schema- 0.84, positive other- 0.84 and negative other- 0.87. Similarly high coefficients have been found in non-clinical samples: positive self-schema- 0.78, negative self-schema- 0.86, positive other- 0.88 and negative other- 0.88 (Fowler et al., 2006b). In terms of its convergent validity with other measures, the negative-self and positive-self subscales of the BCSS have been found to have moderate to strong associations with the total score from the Rosenberg Self-Esteem Scale (RSES; Rosenberg, 1965) within a sample of participants with psychosis ($r=0.64$ and 0.65 , respectively) (Fowler et al., 2006b). However, correlations between the total score on the RSES and BCSS negative-other and positive-other subscales in the aforementioned clinical sample have been found to be weak ($r=0.2$ and -0.26 , respectively) (Fowler et al., 2006b). The test-retest reliability of the BCSS has been tested in a non-clinical sample of 257 students on two occasions, approximately three weeks apart (Fowler et al., 2006b). Each subscale was found to be stable with the following Pearson's r reported: negative-self ($r=0.84$), positive-self ($r=0.82$), negative-other ($r=0.7$) and positive-other ($r=0.72$).

Composition for analysis

Due to the non-normal distribution of this data, total sample median-splits were used to dichotomise total scores for negative self (1 or more = present) and negative other (3 or more = present), positive self (13 or more = present) and positive other (12

or more = present), into new binary variables for use in logistic regression and synergistic effects analyses.

4.5.2. Hamilton Depression Scale (HAM-D; Hamilton, 1960)

This is one of the earliest scales to be developed for depression and was created to be a clinician-rated scale aimed at assessing the severity of depression amongst patients. The 17-item version has become the gold-standard used in clinical trials, and is now the most widely used scale in controlled clinical trials in depression (Baer & Blais, 2010).

The HAM-D is used to measure depressive symptoms experienced over the past seven days and a structured interview guide has been developed to improve inter-rater reliability (SIGH-D; Williams, 1988; 1992). The scale consists of 17 items and rates the severity of symptoms such as low mood, insomnia, agitation, anxiety and weight loss. A copy is provided in Appendix G. The total score is obtained by summing the score of each item, 0-4 (symptom is absent, mild, moderate or severe), or 0-2 (absent, slight, clearly present), and the total scores can range from 0-54. It is accepted by most clinicians that scores ranging from 0 to 6 do not indicate the presence of depression, scores between 7 and 17 indicate mild depression, scores between 18 and 24 indicate moderate depression, and scores over 24 indicate severe depression (Baer & Blais, 2010).

Psychometric properties

The HAM-D is a multidimensional scale, and this implies that the score of a specific item cannot be considered a good predictor of the total score (Bech, 2002). It also means that identical total scores from two different patients may have different clinical meanings, as high ratings on a few items can yield the same score as a lower rating on many items (Bech et al., 2002). A number of studies have shown the internal consistency of different versions of the HAM-D to range from 0.48 to 0.92 (Hamilton et al., 2000), but a review paper showed that the majority of HAM-D items have adequate reliability (Bagby et al., 2004). However, inter-rater reliability has been found to be very high for HAM-D total scores (0.80-0.98), even if it may show lower reliability for individual items, and all items showed adequate reliability when the scale was

administered according to the interview guidelines (Moberg et al., 2001). The test-retest reliability for the HAM-D alongside use of the SIGH-D has been reported to be as high as 0.81, its validity has been reported to range from 0.65 to 0.90, and it has been shown to be highly correlated with other clinical measures of depression (Hamilton, 2000).

Composition for analysis

The total depression score was calculated for each participant and due to the scores being highly positively skewed, the total sample median split (4 or more = present) was used to dichotomise the continuous score into a new binary variable for use in logistic regression and mediation analyses.

4.5.3. Hamilton Anxiety Scale (HAM-A; Hamilton, 1959, 1969)

The HAM-A was developed as a clinician-administered, typically semi-structured interview designed to assess anxiety symptoms not specific to any disorder (Hamilton, 1959; 1969). It is used to measure anxiety symptoms experienced over the past seven days and a structured interview guide is also available for interviewers to consider, the Hamilton Anxiety Rating Scale (SIGH-A; Shear et al., 2001), which has demonstrated adequate reliability and validity. The scale consists of 14 items that measure both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). A copy is provided in Appendix H. Each item is rated on a scale from 0 (not present) to 4 (very severe/incapacitating). A total score (out of a possible 56) is obtained by summing the 14 items (higher scores indicating more anxiety). In addition to a total score, the sum of the two subscales, the psychic subscale (sum of items 1-6 and 14), and the somatic subscale (sum of items 7-13), can also be created. Total scores above 16 are generally considered indicative of symptomatic Generalised Anxiety Disorder (Hamilton, 1959).

Psychometric properties

Internal consistency for the HAM-A has ranged from adequate (α values of 0.77 to 0.81; Moras et al., 1992) to excellent (α = 0.92; Kobak et al., 1993), depending on the study considered. The HAM-A has also demonstrated excellent one week test-retest reliability (α = 0.96; Maier et al., 1988). Inter-rater reliability of the original study was

strong ($\alpha = 0.89$; Bruss et al., 1994), but subsequent studies have demonstrated lower estimates (e.g. $\alpha = 0.65$; Moras et al., 1992).

Composition for analysis

The total anxiety score was calculated for each participant and due to the scores being highly positively skewed, the total sample median split (5 or more = present) was used to dichotomise the continuous score into a new binary variable for use in logistic regression and mediation analyses.

4.6. Statistical Analysis

4.6.1. Sample size calculation

Initial power calculations were performed assuming a final sample of at least 200 cases and 200 controls. Conservatively assuming a prevalence of exposure to life events in the preceding year of 0.30 in cases and 0.15 in controls, it was calculated that this sample size would have over 90% power to detect what is a difference in proportions of 0.15 (i.e., an odds ratio of 2.4). With a sample of 400, using a conservative rule allowing for one parameter for every 20 subjects, this would allow up to 20 variables to be entered into regression, interaction and mediation models. The final sample included in this thesis was actually larger than first anticipated (253 cases and 301 controls completed the LEDS measure), and so the final sample size appears justified for these analyses.

4.6.2. Explanation of survey weights

For the wider CAPsy study, black Caribbean and black African controls were oversampled to ensure a sufficient number for sub-analyses by ethnicity. Before commencing the data analysis for this thesis, inverse sampling probability weights were generated to account for oversampling (i.e., to standardise and weight black Caribbean and black African controls back to their population proportions). Weights were constructed based on any differences between demographic features of the control sample (age, gender and ethnicity), and features of the local population (based on data

from the 2011 UK Census). The procedure for weighting an individual was as follows (where ‘a’ could represent gender, ‘b’ could represent ethnicity and ‘c’ could represent age):

$$Weight = \frac{P(a) \text{ in population}}{P(a) \text{ in sample}} \times \frac{P(b) \text{ in population}}{P(b) \text{ in sample}} \times \frac{P(c) \text{ in population}}{P(c) \text{ in sample}}$$

The above method ensured demographic groups would receive different weighting according to the degree to which they had been under- or over-sampled. These weights were consequently applied in all analyses to account for this oversampling using the survey options in Stata (or the `iweight` or `pweight` commands). Using weights in the analyses ensures that any biases that might have resulted from oversampling are adjusted for. In other words, it ensures that, in the analyses, the proportions in each age, ethnic, and sex group in the control sample are in line with the proportions in the general population.

4.6.3. Analysis of Chapter 5

Sample characteristics

Independent sample t-tests and chi-square tests were used to describe sociodemographic differences between cases and controls. Descriptive analyses of continuous variables across three-groups (e.g. cases, controls with PLE, and controls without PLE) were assessed using one-way ANOVAS. Where appropriate throughout the analyses, continuous independent variables were checked for normal distribution using visual inspection of histograms, and for their skew and kurtosis.

4.6.4. Analysis of Chapter 6

Main effects of life events and difficulties

To test the main effect of adult life events and difficulties on odds of psychosis (Hypothesis 1.1), the total number of life events and difficulties experienced were firstly described using their median values and interquartile range (IQR) (due to non-normal

distributions), and the association with case status was analysed using the Wilcoxon rank-sum test (unable to be weighted). Logistic regression was then used to analyse the relationship between the prevalence of life events and difficulties and odds of psychosis, with case-control status as the main outcome variable. Logistic regression was also used to analyse the relationship between further characteristics within the life events and difficulties data, and case-control status (Hypotheses 1.2, 1.4-1.7). These analyses investigated whether the odds of psychosis were influenced by the severity, intrusiveness, independence, focus, and timing of the events and difficulties experienced. Multinomial logistic regression was used to assess the impact of severity on PLE across cases (coded as 2), controls with PLE (coded as 1), and controls without PLE (coded as 0) (Hypothesis 1.3). The reference group was changed to 1 (indicating controls with PLE), when comparing cases with controls with PLE. All analyses controlled for the following *a priori* confounders: gender (male or female), age (continuous), ethnicity (White British, White Other, Black Caribbean, Black African, Asian (all), or Other), and subject main social class (salariat, intermediate, working class, long-term unemployed, student, non-classifiable).

Additional models

Where power allowed (i.e. for analyses of event/difficulty severity and intrusiveness), analyses were also repeated after adjusting for additional variables which showed an observed association with case-control status (i.e. current cannabis use and family history of psychosis). Additional models were created which adjusted for *a priori* confounders and also current cannabis use, and family history of psychosis, in a smaller sample to see whether the effects of severity and intrusiveness remained after controlling for these additional potential confounders. These two variables were entered consecutively into the model along with the *a priori* confounders.

Interactions by age and gender

In addition, the main effects analyses of severity and intrusiveness were repeated stratified by gender, and age at the time of assessment, and interaction term *p*-values were used to determine interaction effects. The interaction term *p*-values were used to assess the presence of effect modification as it is not possible to calculate robust standard errors for a likelihood ratio test, which are required when using weighted data.

The p -value for the interaction term is the same as would be produced for the likelihood ratio test. A more liberal approach was taken to p -values when analysing interaction (and further synergistic effects in Chapter 7) because these are more difficult to detect. This was to ensure that no potential interaction/synergistic effects were missed. However, it is noted that although this approach aims to avoid type II errors (i.e. failing to find a true effect), minimising the risk of these errors increases the risk of type I error (i.e. reporting an effect when one does not exist), so with this in mind, any effects where $p > 0.05$ were cautiously reported.

Further exploratory analyses

In terms of further exploratory analyses, logistic regression was used to assess the influence of difficulty duration on case-control status, and multinomial logistic regression was used to assess the impact of intrusive events and difficulties on PLE status. The GAF scores across cases exposed to and not exposed to severe life events were presented using the median and IQR and associations between life events/difficulties and symptom severity in cases was analysed using the Wilcoxon rank-sum test.

4.6.5. Analysis of Chapter 7

Schematic beliefs, affective symptoms and case-control status

To examine the associations between schemas and case-control status/PLE status (Hypotheses 2.1 and 2.2), the median values and IQR were presented, and logistic and multinomial regression were used to assess associations with case status using the binary schema variables cut at the median. These analyses were firstly conducted unadjusted and then adjusted for *a priori* and additional confounders. To examine the associations between affective symptoms and case-control status/PLE status (Hypotheses 4.1 and 4.2), the median values and IQR were presented, and logistic and multinomial regression were used to assess associations with case status using the binary affective symptom variables cut at the median. These analyses were firstly conducted unadjusted and then adjusted for *a priori* and additional confounders.

Justification for using median splits

In order to explore associations between schemas, affective symptoms and psychosis, the continuous schema scores (scored from 0-24) and the anxiety (scored from 0-56) and depression scores (scored from 0-54) were recoded to form binary variables. The total sample median was assessed and median splits were used to dichotomise total scores for negative self (1 or more = present) and negative other (3 or more = present), positive self (13 or more = present) and positive other (12 or more = present), anxiety symptoms (5 or more = present) and depression symptoms (4 or more = present). It is acknowledged that using the overall sample median-split may restrict the comparisons as different cut points exist for cases and controls, and that dichotomisation may lead to a loss in statistical power (MacCallum et al., 2002; DeCoster et al., 2009). However, this approach is in line with previous research studies that have investigated the impact of cognitive and affective processes on the relationship between stressful experiences and psychosis (e.g. Fisher et al., 2012). Furthermore, a dichotomised indicator is assumed to perform better when the underlying latent variable is highly skewed, and can be beneficial when a variable is not linearly related to an outcome (Farrington & Loeber, 2000). Therefore, due to the skewed distribution of these variables and the non-linear relationship between the potential predictors and outcome, this approach does appear to be justified. Another important criteria when deciding whether to dichotomise variables is to ensure that the observed measure has high reliability (DeCoster et al., 2009, 2011). All of the measures used to assess affective symptoms and schemas have been shown to have good psychometric properties and show stability over time (Maier et al., 1988; Moberg et al., 2001; Fowler et al., 2006b). Finally, it could also be argued that categorising variables can improve the communication of research findings by making results more interpretable and easier to understand (e.g. Farrington & Loeber, 2000).

Interactions with social class and negative schemas

To examine whether exposure to severe life events and difficulties combined synergistically with lower social class status to increase the odds of psychotic disorder (Hypothesis 3.1), interaction contrast ratios (ICRs) were used to test for interaction on an additive scale, (i.e. for departure from additivity), as described by Schwartz (2006). Evidence of a potential interaction was indicated by an ICR of greater than zero. Confidence intervals (CIs) and p-values for ICRs were generated using the NLCOM

command in Stata (StataCorp, 2009). Additive models test the combined (synergistic) effect of two variables on odds or risk of a disorder. As such, they are usually referred to as synergistic effects or models. Therefore, this thesis will refer to the terms additive interaction, synergy and synergistically interchangeably.

To examine if there was evidence that exposure to severe life events and difficulties combined synergistically with negative schemas about the self and others (Hypothesis 3.2) to increase the odds of psychosis, ICRs were also used to test for interaction on an additive scale. For the purposes of these analyses, the dichotomised threatening event/difficulty variables (based on event and difficulty severity) were used, and analysed with the dichotomised negative-other and negative-self variables (cut at the median). These synergistic effects analyses were completed for cases vs. controls and for controls with PLE vs. controls without PLE.

Justification for using additive vs. multiplicative model

When assessing for the presence of an interaction between two variables, there are two possibilities in terms of analysis- either test for an interaction on an additive or a multiplicative scale. When there is interaction in terms of the difference measure of association, or the risk difference, this is evidence for an additive interaction, e.g. there is an added increase in disease risk when individuals are exposed to two risk factors beyond what would be expected from the impact of the risk factors on their own. When there is interaction in terms of the ratio measure of association, then this is a multiplicative interaction, e.g. the risk of disease is multiplied in individuals with the risk factor(s) compared with those without. Research suggests that it is statistically possible to find an interaction on one scale and not on another (Zammit et al., 2010), which suggests that interactions are scale-dependent. From this perspective, it was important to take an *a priori* approach based on theoretical assumptions from epidemiology and the work of Sharon Schwartz (Schwartz, 2006). With these assumptions in mind, it was decided that this thesis would test for interaction on an additive scale rather than multiplicative one. My decision to model interactions between life events, schemas and social class on an additive scale was made because, within a minimum sufficient causes framework, additive models provide the best representation of the combined effect of two variables (i.e. synergy or additive interaction) (Rothman et al. 1980; Schwartz, 2006). Others have also suggested that multiplicative models are more complex and prone to error and, from a public health perspective, they are not as

informative as additive models, which provide more readily interpretable information on the combined impact of two risk factors over and above what would be expected from each one alone (Kendler & Gardner, 2010).

Mediation analyses

The potential mediating effect of affective processes, i.e. levels of depression and anxiety (Hypothesis 4.3), were assessed using the `binary_mediation` command in Stata. These analyses were conducted using the dichotomised severe life event and difficulties variables and the dichotomised variables for anxiety and depression levels (cut at the median). The mediation analyses were completed for cases vs. controls and for controls with PLE vs. controls without PLE. Standardised coefficients were reported for the indirect effects of anxiety and depression, the direct effects, and the total effects, along with their 95% confidence intervals. These were calculated using the bootstrap command with 500 bootstrap replications, and the bias-corrected confidence intervals were reported. These mediation analyses were unable to be weighted.

All analyses were conducted using Stata version 11.2 (StataCorp, 2009).

CHAPTER 5 - Sample Characteristics

Synopsis

This chapter will begin by comparing demographic characteristics between cases and controls within the full CAPsy study sample. The demographic characteristics will be presented for three different time points: at interview (for cases and controls), at the point of psychosis onset (cases only), and one year pre-onset (cases) or one year pre-interview (controls). This will be followed by a comparison of demographic characteristics for cases who completed the LEDS interview and for cases with missing LEDS assessments. The chapter will then present the characteristics of controls who reported low level psychotic experiences and compare these with cases and other controls without psychotic experiences.

5.1. Sample demographics results

5.1.1. Comparison between cases and controls on current demographic variables for the total sample

A final screened sample of 885 cases were potentially eligible to be approached for participation in the CAPsy study. Due to many cases being missed before the researchers could have any direct contact (e.g. they did not attend appointments where the study could be introduced, or they moved out of the area), of the 885 possible cases, 557 were approached to take part, and 328 cases were consented to the study. Of those cases who consented, 25 dropped out before any assessments were completed, leaving a final total sample of 303 cases and 301 controls. The 25 cases who dropped out were compared with the final total case sample (n=303) on basic demographics (age, gender, ethnicity, highest level of education) see Table 5.1. Those who dropped out after consent were older than cases who completed assessments (drop-out cases mean age: 32.3 years (SD: 11.24) vs. complete cases: 28.9 years (SD: 8.71); $p=0.07$), and drop-out cases were less likely to be male (male drop-out cases 48% vs. male complete cases 63%; $p=0.137$). Furthermore, there do appear to be some differences with regard to ethnicity, e.g. drop-out cases were less likely to be Black African (drop-out cases 16% vs. complete cases 26.1%; $p=0.286$), or Black Caribbean (drop-out cases 4% vs. complete cases 17.2%; $p=0.286$). In terms of differences in highest educational

attainment, cases who completed assessments were also more likely to have completed further/vocational courses compared with drop-out cases (drop-out cases 23.8% vs. complete cases 43.1%; $p=0.218$). These differences may reflect the characteristics of individuals who are more likely to be granted earlier discharge from inpatient units and therefore be missed when completing research assessments after consent, i.e. they may be more likely to be older, female, and of white ethnicity.

Table 5.1 Comparison of socio-demographic characteristics between psychosis cases who did and did not drop-out of the study

	Completers (n=303)	Drop-outs (n=25)	<i>t</i>	df	<i>p</i>
	Mean (SD)	Mean (SD)			
Age in years	28.9 (8.71)	32.3 (11.24)	1.83	326	0.07
	n (%)	n (%)	χ^2	df	<i>p</i>
Sex					
Male	191 (63.0)	12 (48.0)	2.21	1	0.137
Female	112 (37.0)	13 (52.0)			
Ethnicity					
White British	81 (26.7)	9 (36.0)	6.21	5	0.286
White Other	39 (12.9)	5 (20.0)			
Black African	79 (26.1)	4 (16.0)			
Black Caribbean	52 (17.2)	1 (4.0)			
Asian (all)	11 (3.6)	2 (8.0)			
Other	41 (13.5)	4 (16.0)			
Highest level of education (<i>4 missing values</i>)					
Higher	60 (19.9)	5 (23.8)	3.04	2	0.218
Further	130 (43.1)	5 (23.8)			
School	112 (37.1)	11 (52.4)			

df, degrees of freedom. SD, standard deviation. (Percentages may not add up to 100 due to rounding).

Within the total sample who were administered the socio-demographic schedule (303 cases and 301 controls), the following observations were made about demographic variables at the time of interview: compared with controls, cases were younger (mean age in cases 28.9 years vs. weighted mean age of 37.0 years in controls; $p<0.001$), more often men (cases 63% vs. controls 50.1%; $p=0.003$), more often of non-White ethnicity ($p<0.001$), and more likely to have a lower level of education (i.e. school leavers with or without qualifications) (cases 37.1% vs. controls 12.3%; $p<0.001$) (see Table 5.2). Furthermore, in terms of parental social class and main subject social class, the parents of cases and the cases themselves were less likely to be in the highest social class category compared with controls ($p<0.001$)- see Table 5.2. There was a noticeable shift when looking at current social class as the majority category for cases was long-term unemployed (cases 46.9% vs. controls 8.5%; $p=0.001$). Furthermore, compared with controls, cases were more likely to have a family history of any mental illness in a first degree relative (cases 47.9 % vs. controls 39.6%; $p=0.094$), and a family history of psychosis in a first degree relative (cases 16% vs. controls 6.4%; $p=0.018$). Cases were more likely than controls to have ever tried cannabis (cases 74.5% vs. controls 61.3%; $p=0.003$), and were more likely to be currently using cannabis (cases 29.1% vs. controls 16.4%; $p=0.003$).

Further demographic variables (i.e. employment status, relationship status and living arrangement) were analysed at one year pre-onset/interview and at onset (cases only) to give an indicator of the types of events and difficulties the participants may be exposed to during the LEDS period, e.g. if proportions of cases reporting to be single has changed over this time point, then we would expect to see an abundance of relationship events occurring within this group. For completeness of this analysis and to see whether there are any signs of social drift, I have also presented information about these variables at the time of interview in Table 5.2. Cases were more likely to be currently unemployed (cases 56% vs. controls 13%; $p<0.001$), which is not surprising given the majority social class rating for cases. Cases were also more likely to be single compared with controls (cases 75.6% vs. controls 34.1%; $p<0.001$), and were less likely to be living with others (cases 69.6% vs. controls 77.5%; $p=0.043$).

Table 5.2 Current socio-demographic characteristics of cases and controls

	Cases (n=303)	Controls (n=301)		<i>t</i> *	df*	<i>p</i> *
	Mean (SD)	Mean (SD)	Weighted Mean (SD)			
Age in years	28.9 (8.71)	35.3 (12.34)	37.0 (12.20)	-8.80	603	<0.001
	n (%)	n (w%)		<i>χ</i> ² *	df*	<i>p</i> *
Sex						
Male	191 (63.0)	153 (50.1)		10.24	1	0.003
Female	112 (37.0)	148 (49.9)				
Ethnicity						
White British	81 (26.7)	131 (42.6)		39.51	5	<0.001
White Other	39 (12.9)	36 (19.5)				
Black African	79 (26.1)	49 (12.7)				
Black Caribbean	52 (17.2)	44 (11.2)				
Asian (all)	11 (3.6)	15 (6.3)				
Other	41 (13.5)	26 (7.8)				
Current employment status (5 missing values)						
Employed	64 (21.5)	194 (68.0)		153.76	3	<0.001
Student	31 (10.4)	38 (9.8)				
Unemployed	167 (56.0)	43 (13.0)				

	Cases (n=303) n (%)	Controls (n=301) n (w%)	χ^2*	df*	p^*
Economically inactive	36 (12.1)	26 (9.2)			
Highest level of education (<i>3 missing values</i>)					
Higher	60 (19.8)	165 (56.7)	97.40	2	<0.001
Further	130 (42.9)	96 (31.1)			
School	113 (37.3)	38 (12.3)			
Parental social class (birth)					
Salariat	77 (25.4)	154 (52.2)	54.49	5	<0.001
Intermediate	72 (23.8)	54 (18.0)			
Working Class	87 (28.7)	60 (20.1)			
Student	2 (0.7)	3 (0.8)			
Long-term unemployed	3 (1.0)	5 (1.7)			
Non-classifiable	62 (20.5)	25 (7.3)			
Parental social class (main)					
Salariat	85 (28.1)	157 (50.9)	52.49	4	<0.001
Intermediate	80 (26.4)	87 (28.2)			
Working Class	92 (30.4)	52 (17.3)			
Long-term unemployed	3 (1.0)	0 (0.0)			
Non-classifiable	43 (14.2)	5 (3.6)			

	Cases (n=303) n (%)	Controls (n=301) n (w%)	χ^2 *	df*	p *
Subject social class (current)					
Salariat	13 (4.3)	119 (41.9)	194.21	5	<0.001
Intermediate	38 (12.5)	64 (23.1)			
Working Class	49 (16.2)	24 (6.7)			
Student	29 (9.6)	39 (10.1)			
Long-term unemployed	142 (46.9)	28 (8.5)			
Non-classifiable	32 (10.6)	27 (9.6)			
Subject social class (main)					
Salariat	31 (10.2)	150 (53.8)	177.45	5	<0.001
Intermediate	79 (26.1)	76 (25.6)			
Working Class	135 (44.6)	37 (10.7)			
Student	22 (7.3)	32 (7.8)			
Long-term unemployed	26 (8.6)	1 (0.2)			
Non-classifiable	10 (3.3)	5 (1.9)			
Relationship status (current) (4 missing values)					
In a relationship	73 (24.4)	191 (66.0)	104.57	1	<0.001
Single	226 (75.6)	110 (34.1)			
Living arrangement (current) (4 missing values)					
With others	208 (69.6)	235 (77.5)	4.84	1	0.043

	Cases (n=303)	Controls (n=301)	χ^2*	df*	p^*
	n (%)	n (w%)			
Alone	91 (30.4)	66 (22.5)			
Family history of any mental illness (127 missing values)					
No	110 (52.1)	164 (60.4)	3.29	1	0.094
Yes	101 (47.9)	102 (39.6)			
Family history of psychosis (140 missing values)					
No	168 (84.0)	252 (93.6)	11.00	1	0.018
Yes	32 (16.0)	12 (6.4)			
Ever used cannabis (98 missing values)					
No	59 (25.5)	106 (38.7)	9.87	1	0.003
Yes	172 (74.5)	169 (61.3)			
Current cannabis use (99 missing values)					
No	163 (70.9)	230 (83.6)	11.71	1	0.003
Yes	67 (29.1)	45 (16.4)			

df, degrees of freedom. SD, standard deviation. w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). *, calculated using weights. Figures in bold indicate $p < 0.05$. (Percentages may not add up to 100 due to rounding).

5.1.2. Comparison between cases and controls on demographic variables at other time points

As was found for current social factors, cases differed from controls in terms of employment status, whether they were in a relationship and their living arrangement at other time points, although the differences were not quite as striking as what was reported for the time of interview - see Tables 5.3 and 5.4. Cases and controls were compared for the period one year prior to onset/interview but demographic information at onset was available for cases only as there was not a comparable period for controls.

At one year prior to onset, cases were still found to have higher levels of unemployment compared with controls (cases 30.9% vs. controls 8.9%; $p < 0.001$). For cases only, we can see that there is likely to be an increase in unemployment during the year prior to onset, with the proportion at onset being reported to be 40.2%, and there were even further increases between onset and interview (current unemployment reported by 56% of cases). As reported for their current situation, cases were more likely to be single one year prior to onset compared with controls (cases 62.5% vs. controls 32.8%; $p < 0.001$). For cases only, we can see that there is a small increase in the number of people reporting to be single during the year prior to onset (69.4%), with an even further increase in the period between onset and interview (75.6%). Interestingly, when considering living arrangement, there did not appear to be any differences between cases and controls at one year pre-onset/interview. In cases, the proportions decreased by a small amount in the year period leading up to onset as slightly more cases were living alone at the time of onset. These figures appeared to increase slightly in the period between onset and interview as at the point of interview, case-control differences in living arrangement had reached standard levels of significance, and cases were more likely to be living alone compared with controls.

For cases, there looks to be a pattern of deterioration in social circumstances across each of the time points considered, i.e. a worsening of social circumstances from one year pre-onset to onset, and again from onset to the point of interview, whereas these differences were not observed for control subjects, whose social circumstances appeared to remain relatively stable across time. This pattern of deterioration has also been shown in other first-episode studies (Stilo et al., 2013).

Table 5.3 Socio-demographic characteristics of cases at the time of onset

	Cases (n=303) n (%)
Employment status at onset (15 missing values, 17 N/A)	
Employed	103 (38.0)
Student	36 (13.3)
Unemployed	109 (40.2)
Economically inactive	23 (8.5)
Relationship status at onset (15 missing values, 17 N/A)	
In a relationship	83 (30.6)
Single	188 (69.4)
Living arrangement at onset (12 missing values, 17 N/A)	
With others	197 (71.9)
Alone	77 (28.1)

(Percentages may not add up to 100 due to rounding).

Table 5.4 Socio-demographic characteristics of cases and controls one year pre-onset/interview

	Cases (n=303) n (%)	Controls (n=301) n (w%)	χ^2 *	df*	p *
Employment status 1 year pre-onset/interview (14 missing values, 20 N/A)					
Employed	127 (47.2)	208 (71.9)	51.93	3	<0.001
Student	40 (14.9)	40 (10.7)			
Unemployed	83 (30.9)	29 (8.9)			
Economically inactive	19 (7.1)	24 (8.5)			
Relationship status 1 year pre-onset/interview (14 missing values, 20 N/A)					
In a relationship	101 (37.6)	193 (67.2)	50.09	1	<0.001
Single	168 (62.5)	108 (32.8)			
Living arrangement 1 year pre-onset/interview (14 missing values, 20 N/A)					
With others	200 (74.4)	237 (77.8)	0.90	1	0.380
Alone	69 (25.7)	64 (22.3)			

df, degrees of freedom, w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). *, calculated using weights. Figures in bold indicate $p < 0.05$. (Percentages may not add up to 100 due to rounding).

5.1.3. Comparison of demographic characteristics of LEDS completers and non-completers (cases only)

For the majority of participants, a LEDS interview was completed (n=554, 92%). All 301 control participants completed the LEDS but there were some case participants with missing LEDS assessments (n=75), which gave a total LEDS case sample of 253 participants. The main reason for an uncompleted LEDS within the case subjects was that we were unable to contact them after their initial consent, and therefore they only completed initial or earlier assessments (n=56). As the LEDS is primarily designed for adult samples, we decided not to complete a LEDS assessment with those whose psychosis began in childhood (i.e. prior to 17 years) (n=16). There was also one case participant who refused to complete the LEDS interview, and two case participants who were too unwell to take part in the interview, and subsequently could not be completed at a later date.

Table 5.5 compares those who completed the LEDS, those who did not, and those who had onset in childhood on a number of demographic characteristics. There were no substantial differences found between completers and non-completers with regard to age at interview. However, the subjects whose onset began in childhood were unsurprisingly younger than the other two groups. With regard to gender, the completers and non-completers again did not differ considerably, but the childhood onset cases were more likely to be male (75% of the sample). As with age and gender, there were no differences between the completers and non-completers in terms of ethnicity, but childhood onset cases were more likely to be white British. Completers were more likely to have attended higher education, achieving either a university degree or MSc/PhD study compared with non-completers (completers 22.2% vs. non-completers 12.7%). In terms of social class, it appears that non-completer groups are more likely to be in the working class category compared with completers (completers 40.7%; non-completers (not childhood onset) 65.7%; non-completers (childhood onset) 56.3%).

Table 5.5 Comparison of socio-demographic characteristics of LEDS completers and non-completers (cases only)

	Completers (n=253)	Non- completers (n=59)	Non- completers (childhood onset) (n=16)	<i>F</i>	<i>df</i>	<i>p</i>
	Mean (SD)	Mean (SD)	Mean (SD)			
Age in years	29.0 (8.85)	30.7 (9.17)	26.4 (9.24)	1.77	327	0.172
	n (%)	n (%)	n (%)	χ^2	<i>df</i>	<i>p</i>
Sex						
Male	156 (61.7)	35 (59.3)	12 (75.0)	1.34	1	0.529
Female	97 (38.3)	24 (40.7)	4 (25.0)			
Ethnicity						
White British	70 (27.7)	14 (23.7)	6 (37.5)	7.92	5	0.677
White Other	32 (12.7)	11 (18.6)	1 (6.3)			
Black African	65 (25.7)	13 (22.0)	5 (31.3)			
Black Caribbean	45 (17.8)	7 (11.9)	1 (6.3)			
Asian (all)	10 (4.0)	3 (5.1)	0 (0.0)			
Other	31 (12.3)	11 (18.6)	3 (18.8)			
Employment status 1 year pre-onset (39 missing values, 6 completers & 33 non-completers, 4 N/A)						
Employed	117 (47.6)	10 (43.5)	n/a	1.14	3	0.793
Student	35 (14.2)	5 (21.7)	n/a			
Unemployed	76 (30.9)	7 (30.4)	n/a			
Economically inactive	18 (7.3)	1 (4.4)	n/a			
Highest level of education (4 missing values, 4 non-completers)						
Higher	56 (22.1)	7 (12.7)	2 (12.5)	3.82	2	0.452
Further	105 (41.5)	24 (43.6)	6 (37.5)			
School	92 (36.4)	24 (43.6)	8 (50.0)			
Subject social class (main) (24 missing values, 24 non-completers)						
Salariat	28 (11.1)	2 (5.7)	1 (6.3)	11.31	5	0.359
Intermediate	71 (28.1)	5 (14.3)	3 (18.8)			
Working Class	103 (40.7)	23 (65.7)	9 (56.3)			
Student	20 (7.9)	1 (2.9)	1 (6.3)			
Long-term unemployed	22 (8.7)	2 (5.7)	2 (12.5)			
Non-classifiable	9 (3.6)	2 (5.7)	0 (0.0)			

df, degrees of freedom, SD, standard deviation. (Percentages may not add up to 100 due to rounding).

Prevalence of psychotic-like experiences (PLE) within controls

The individual item break down for the PSQ questions is given in Table 5.6. The figures and percentages highlighted in the last column are what I have used to derive the PLE subgroup. Forty (11.5%) controls reported recent subclinical psychotic experiences and 38 (11.1%) controls reported these experiences when hypomania was excluded. In line with previous studies, the hypomania questions were not included when analysing the impact of PLE status for all subsequent analyses in this thesis (Wiles et al., 2006; Morgan et al., 2009).

5.1.4. Comparison between psychosis cases, controls with PLE and controls without PLE on sample demographics

Table 5.7 compares cases, controls with PLE, and controls without PLE on a number of demographic characteristics. As in the main case-control sample, cases were considerably younger than both controls groups with and without PLE. The two control groups were found to have a similar mean age (weighted mean age of controls with PLE 37.1 years vs. controls without PLE 36.9 years; $p < 0.001$). Differences in gender were also found between cases and controls, with cases being more likely to be male, although there were no differences found between the two control groups ($p = 0.01$). More stark differences were found with regard to ethnicity. Controls with PLE were far less likely to be of white British ethnicity compared with cases and controls without PLE (white British cases 26.7% vs. controls with PLE 13.0% vs. controls without PLE 46.2%; $p < 0.001$), and were more likely to come from minority ethnic backgrounds, such as black African (24.2%) and black Caribbean (22%).

Both control groups were not found to differ in terms of current employment status, and the overall group differences mirror the main case-control sample. In terms of highest level of education, controls with PLE were less likely to have attained a higher education level compared with controls without PLE. When considering parental social class at the time of subjects' birth, case parents were least likely to be in the highest social class category, and controls with PLE fell roughly in the middle of the other two groups (cases 25.4% vs. controls with PLE 40.5% vs. controls without PLE 53.6%, $p < 0.001$).

Table 5.6 Prevalence of positive responses to PSQ items within the controls sample

PSQ Items	'Yes' Responses n (w%) (bold indicates no. reporting PLE)
Initial probe	
<i>Secondary questions</i>	
Hypomania	
(1A) ...times when you felt very happy indeed without a break...	143 (46.2)
<i>(1B) ...obvious reason for this</i> (n and % are for 'no' responses)...	25 (6.0)
<i>(1C) ...relatives or friends think it was strange or complain ...</i>	4 (1.1)
Thought Insertion	
(2A) ...ever felt thoughts were interfered with or controlled ...	17 (4.8)
<i>(2B) ...in a way that many people would find hard to believe ...</i>	3 (0.9)
Paranoia	
(3A) ...times when people were against you...	75 (23.6)
<i>(3B) ...times when people deliberately acting to harm you</i>	27 (8.1)
<i>(3C) ... times when group plotting to cause you serious harm ...</i>	2 (0.4)
Strange Experiences	
(4A) ...times when you something strange was going on	37 (10.5)
<i>(4B) ...so strange people would find it very hard to believe</i>	17 (4.5)
Hallucinations	
(5A) ...times when you heard or saw things others couldn't	8 (2.5)
<i>(5B) ...hear voices when no-one around ...</i>	0 (0.0)
Any psychotic experience	40 (11.5)
Any psychotic experience excluding hypomania	38 (11.1)

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). (Percentages may not add up to 100 due to rounding).

A similar pattern is also observed when considering the main parental social class. In terms of main subject social class, cases were least likely to be in the highest social class category compared with the other two groups, but controls with PLE had fewer subjects in the highest category compared to controls without PLE (cases 10.2% vs. controls with PLE 33.2% vs. controls without PLE 56.4%; $p < 0.001$).

In terms of current social factors, both cases and controls with PLE were more likely to be single compared with controls without PLE (cases 75.6% vs. controls with PLE 64.9% vs. controls without PLE 30.2%, $p<0.001$). Controls with PLE were most likely to be living alone (living alone in cases 30.4% vs. controls with PLE 44.5% vs. controls without PLE 19.8%, $p=0.003$).

Furthermore, as with the main case-control results, cases were more likely to have a family history of any mental illness in first degree relatives compared with controls without PLE, but the controls with PLE were most likely to have a family history of any mental illness compared with the other two groups (cases 47.9 % vs. controls with PLE 56.4% vs. controls without PLE 37.4%; $p=0.042$). Cases were also more likely to have a family history of psychosis in their first degree relatives compared with controls without PLE, and controls with PLE were found to have a prevalence that was roughly in between the other two groups (cases 16% vs. controls with PLE 11.4% vs. controls without PLE 5.7%; $p=0.039$). Cases were found to be more likely than controls to have ever tried cannabis, and controls with PLE were least likely to have tried cannabis in their lifetime (cases 74.5% vs. controls with PLE 47.5% vs. controls without PLE 63.1%; $p=0.004$). Cases were more likely to be currently using cannabis compared with controls without PLE, and controls with PLE were again, found to be in the middle of the two other groups with regard to current cannabis use (cases 29.1% vs. controls with PLE 21.3% vs. controls without PLE 15.8%; $p=0.007$).

Table 5.7 Comparison of socio-demographic characteristics between psychosis cases, controls with PLE and controls without PLE

	Cases (n=303)	Controls with PLE (n=38)		Controls without PLE (n=263)		<i>F</i> *	df*	<i>p</i> *
	Mean (SD)	Mean (SD)	Weighted Mean (SD)	Mean (SD)	Weighted Mean (SD)			
Age in years	28.9 (8.71)	33.7 (10.39)	37.1 (12.66)	35.6 (12.60)	36.9 (12.16)	39.29	603	<0.001
	n (%)	n (w%)		n (w%)		<i>x</i> ² *	df*	<i>p</i> *
Sex								
Male	191 (63.0)	20 (48.3)		133 (50.4)		10.29	1	0.011
Female	112 (37.0)	18 (51.7)		130 (49.6)				
Ethnicity								
White British	81 (26.7)	5 (13.0)		126 (46.2)		60.71	5	<0.001
White Other	39 (12.9)	6 (31.4)		30 (18.0)				
Black African	79 (26.1)	13 (24.4)		36 (11.2)				
Black Caribbean	52 (17.2)	10 (22.0)		34 (9.9)				
Asian (all)	11 (3.6)	0 (0.0)		15 (7.1)				
Other	41 (13.5)	4 (9.3)		22 (7.6)				
Current employment status (5 missing values)								
Employed	64 (21.5)	25 (65.4)		169 (68.3)		155.22	3	<0.001
Student	31 (10.4)	3 (4.8)		35 (10.4)				
Unemployed	167 (56.0)	8 (19.8)		35 (12.2)				

	Cases (n=303) n (%)	Controls with PLE (n=38) n (w%)	Controls without PLE (n=263) n (w%)	χ^2*	df*	p^*
Economically inactive	36 (12.1)	2 (9.9)	24 (9.1)			
Highest level of education (2 missing values)						
Higher	60 (19.8)	16 (44.0)	149 (58.3)	100.0	2	<0.001
Further	130 (42.9)	16 (40.4)	80 (29.9)			
School	113 (37.3)	6 (15.6)	32 (11.8)			
Parental social class (birth)						
Salariat	77 (25.4)	13 (40.5)	141 (53.6)	58.20	5	<0.001
Intermediate	72 (23.8)	9 (22.3)	45 (17.4)			
Working Class	87 (28.7)	9 (26.1)	51 (19.3)			
Student	2 (0.7)	0 (0.0)	3 (0.9)			
Long-term unemployed	3 (1.0)	0 (0.0)	5 (1.9)			
Non-classifiable	62 (20.5)	7 (11.1)	18 (6.8)			
Parental social class (main)						
Salariat	85 (28.1)	14 (42.1)	143 (52.0)	55.72	4	<0.001
Intermediate	80 (26.4)	14 (29.4)	73 (28.0)			
Working Class	92 (30.4)	10 (28.6)	42 (16.0)			
Long-term unemployed	3 (1.0)	0 (0.0)	0 (0.0)			

	Cases (n=303) n (%)	Controls with PLE (n=38) n (w%)	Controls without PLE (n=263) n (w%)	χ^2*	df*	p^*
Non-classifiable	43 (14.2)	0 (0.0)	5 (4.1)			
Subject social class (current)						
Salariat	13 (4.3)	13 (31.8)	106 (43.1)	201.10	5	<0.001
Intermediate	38 (12.5)	7 (23.8)	57 (23.0)			
Working Class	49 (16.2)	7 (14.5)	17 (5.7)			
Student	29 (9.6)	2 (3.0)	37 (11.0)			
Long-term unemployed	142 (46.9)	8 (18.5)	20 (7.3)			
Non classifiable	32 (10.6)	1 (8.4)	26 (9.8)			
Subject social class (main)						
Salariat	31 (10.2)	11 (33.2)	139 (56.4)	190.77	5	<0.001
Intermediate	79 (26.1)	16 (47.9)	60 (22.8)			
Working Class	135 (44.6)	8 (14.4)	29 (10.3)			
Student	22 (7.3)	3 (4.5)	29 (8.2)			
Long-term unemployed	26 (8.6)	0 (0.0)	1 (0.2)			
Non classifiable	10 (3.3)	0 (0.0)	5 (2.1)			
Relationship status (current) (4 missing values)						
In a relationship	73 (24.4)	16 (35.1)	175 (69.8)	118.83	1	<0.001
Single	226 (75.6)	22 (64.9)	88 (30.2)			

	Cases (n=303) n (%)	Controls with PLE (n=38) n (w%)	Controls without PLE (n=263) n (w%)	χ^2 *	df*	p *
Living arrangement (current) (4 missing values)						
With others	208 (69.6)	23 (55.5)	212 (80.2)	14.02	1	0.003
Alone	91 (30.4)	15 (44.5)	51 (19.8)			
Family history of any mental illness (127 missing values)						
No	110 (52.1)	18 (43.6)	146 (62.6)	7.22	1	0.042
Yes	101 (47.9)	17 (56.4)	85 (37.4)			
Family history of psychosis (140 missing values)						
No	168 (84.0)	31 (88.6)	221 (94.2)	11.87	1	0.039
Yes	32 (16.0)	3 (11.4)	9 (5.8)			
Ever used cannabis (98 missing values)						
No	59 (25.5)	16 (52.6)	90 (36.9)	12.83	1	0.004
Yes	172 (74.5)	19 (47.5)	150 (63.1)			
Current cannabis use (99 missing values)						
No	163 (70.9)	27 (78.7)	203 (84.2)	12.18	1	0.007
Yes	67 (29.1)	8 (21.3)	37 (15.8)			

df, degrees of freedom. PLE, psychotic-like experiences. SD, standard deviation, w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). *, calculated using weights. Figures in bold indicate $p < 0.05$. (Percentages may not add up to 100 due to rounding).

5.2. Summary of Chapter 5

This chapter described the basic demographics of cases and controls at different time-points. Differences between cases and controls were in line with previous research, i.e. cases were younger, more often men, more often from minority ethnic groups, more often disadvantaged and isolated on a number of markers, etc. These findings held at all time-points, with the strongest effects being closer to interview, suggesting some degree of downward social drift in the period pre- and post-onset.

There were few notable differences between cases who completed the LEDS and those who did not. That is, none of the differences reached standard levels of statistical significance and it is unlikely that there are major biases that will influence the findings of this study.

There were some differences between controls who reported low level psychotic experiences and those who did not. The controls with PLE differed from the controls without PLE with regard to ethnicity, education level and family history of any mental illness, and for some variables showed intermediate values between cases and controls without PLE, including parental social class (at subject's birth and main), main subject social class, current relationship status, living arrangement, family history of psychosis, and current cannabis use.

CHAPTER 6 - Life Events & Psychosis: Contexts

Synopsis

This results chapter presents the main effects analyses of life events, difficulties and psychosis, and some further exploratory analyses. It is divided into two parts – firstly, the results from the hypothesis driven analyses are presented and form the main bulk of this chapter, and then secondly, there is a further section detailing the exploratory analyses. The first hypothesis driven section assesses whether experiences of recent events and difficulties are associated with an increased odds of psychotic disorder, independent of potential confounders. The chapter then considers whether specific characteristics of the life events and difficulties data (i.e. their severity, independence, focus, intrusiveness and timing), are differentially associated with psychosis. Potential moderation of the associations by gender and age at the time of assessment are also investigated. The main analyses are repeated for controls with and without psychotic-like experiences (PLE) to explore whether associations hold for sub-clinical phenomena. The second part of this chapter then reports some exploratory analyses, including an investigation of the impact of intrusive events and difficulties on PLE, the effects of difficulty duration, and the impact of severe events and difficulties on general symptom severity.

6.1. Hypotheses

Main effects of life events and difficulties on psychosis:

- 1.1. Recent life events and difficulties will be associated with increased odds of psychosis, independent of *a priori* confounders of age, gender, ethnicity, and social class;
- 1.2. The odds of psychotic disorder will be highest in those who have experienced more severe, more frequent, and more intrusive life events and difficulties;
- 1.3. The odds of psychotic-like experiences will be highest in those who have experienced more severe life events and difficulties;
- 1.4. Associations between severe and intrusive life events, difficulties and psychosis will be modified by gender and age, such that stronger effects will be found for women and younger participants;

- 1.5. Independent life events and difficulties will be associated with an increased odds of psychosis;
- 1.6. The odds of psychosis will be higher in those who have experienced severe events and difficulties which are solely subject focused, compared with exposure to joint and other focused events and difficulties;
- 1.7. The odds of psychosis will be higher in those who have experienced severe life events closest to onset (less than 3 months prior to onset), compared with events occurring at other time points (3-6 months, 6-9 months and 9-12 months prior to the onset of psychosis).

6.2. Analysis plan

All analyses in this chapter were weighted (see Methods chapter for further details of the weighting procedure), unless otherwise stated. Due to a non-normal distribution, the total number of life events and difficulties experienced were described using their median values and interquartile range (IQR) and the association with case status was analysed using the Wilcoxon rank-sum test. As weights were unable to be added to the Wilcoxon rank sum test analyses, the unweighted and weighted median values and IQR for controls were presented for descriptive purposes.

The GAF scores across cases exposed to and not exposed to severe life events were presented using the median and IQR and associations between life events/difficulties and symptom severity in cases was analysed using the Wilcoxon rank-sum test.

The associations between the majority of the life event and difficulties characteristics, i.e. severity, independence, focus, intrusiveness, timing, duration of difficulties, and case-control status, were analysed using logistic regression. These analyses were firstly conducted unadjusted and then adjusted for *a priori* confounders of age, gender, ethnicity, and main subject social class. Where power allowed (i.e. for analyses of event/difficulty severity and intrusiveness), analyses were also repeated after adjusting for additional confounders of current cannabis use and family history of psychosis.

The analyses of life event and difficulty severity and intrusiveness were also performed unstratified, and then stratified by gender and age at the time of assessment.

A more liberal approach was taken to p values when analysing interaction effects because these are more difficult to detect. This was to ensure that no potential interaction effects were missed. However, it is noted that although this approach aims to avoid type II errors (i.e. failing to find a true effect), minimising the risk of these errors increases the risk of type I error (i.e. reporting an effect when one does not exist), so with this in mind, any effects where $p > 0.05$ were cautiously reported.

Multinomial logistic regression was used to assess impact of severity and intrusiveness on PLE across cases (coded as 2), controls with PLE (coded as 1), and controls without PLE (coded as 0). The reference group was changed to 1 (indicating controls with PLE), when comparing cases with controls with PLE.

All analyses were conducted using Stata 11.2.

6.3. Hypothesis driven analyses

6.3.1. How prevalent were life events and difficulties in the one year prior to onset/interview?

In order to address hypothesis 1.1, the first step of the main effects analysis was to assess the prevalence of life events and difficulties in the one year prior to onset/interview, and to see whether these exposures were associated with psychosis, independent of *a priori* confounders of age, gender, ethnicity, and social class.

Contrary to what was hypothesised, controls reported a greater overall number of events and difficulties, at any level of severity, compared with cases. Cases reported a total number of 986 events in the one year period prior to onset and controls reported exposure to 1614 events in total in the one year period prior to interview. In terms of difficulties, controls also reported increased exposure with a total of 871 difficulties across the year period, as opposed to a total of 651 difficulties reported by cases. Due to a non-normal distribution, the median and interquartile range of life events and difficulties among cases and controls is shown in Table 6.1.

Most cases and controls experienced at least one life event and at least one difficulty, at any level of severity, in the year prior to onset or interview (cases 88.6% vs. controls 95.5%), see Table 6.2. After controlling for the effects of *a priori*

confounders, there was evidence to suggest that exposure to both one life event (w.adj. OR 0.38, 95% CI 0.15-0.98, $p=0.045$) and also to two or more life events (w.adj. OR 0.26, 95% CI 0.11-0.58, $p=0.001$) were associated with lower odds of being a case. In terms of difficulties, once *a priori* confounders were taken account of, exposure to either one difficulty (w.adj. OR 0.97, 95% CI 0.45-2.11, $p=0.947$) or to two or more difficulties was not associated with any significant increases in the odds of psychosis (w.adj. OR 0.83, 95% CI 0.42-1.64, $p=0.583$).

Table 6.1 Median number of life events and difficulties in psychosis cases and controls

	Cases (n=253)	Controls (n=301)				
	Median (IQR)	Median (IQR)	Weighted Median (IQR)	<i>z</i>	df	<i>p</i>
Events	3 (2-6)	5 (3-7)	4 (2-7)	4.87	553	<0.001
Difficulties	2 (1-4)	3 (1-4)	3 (1-4)	1.83	553	0.07

z= Wilcoxon rank sum test (unweighted). df, degrees of freedom. IQR, inter-quartile range. Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark.

Table 6.2 Association between number of life events, difficulties and psychotic disorder

		Cases (n=253)	Controls (n=301)					
		n (%)	n (w%)	χ^2 †	df †	p†	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Events								
	No events	29 (11.5)	12 (4.5)	9.50	2	0.022	1	1
	1 event	28 (11.1)	29 (13.0)				0.33 (0.14-0.82)*	0.38 (0.15-0.98)*
	2+ events	196 (77.5)	260 (82.5)				0.37 (0.18-0.77)**	0.26 (0.11-0.58)***
Difficulties								
	No difficulties	33 (13.0)	25 (9.0)	2.69	2	0.315	1	1
	1 difficulty	48 (19.0)	55 (17.7)				0.74 (0.37-1.49)	0.97 (0.45-2.11)
	2+ difficulties	172 (68.0)	221 (73.3)				0.64 (0.35-1.17)	0.83 (0.42-1.64)

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). df, degrees of freedom. †, calculated using weights. OR, odds ratio. CI, confidence interval. *p<0.05; **p<0.01; ***p<0.001. ‡ adjusted for age, gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

6.3.2. *Were more severe events associated with case status?*

In order to address the first part of hypothesis 1.2, the next section assessed whether the odds of psychotic disorder were highest in those who had experienced more severe and more frequent life events and difficulties one year prior to onset.

The previous section suggests that the experience of recent life events and difficulties at any level of severity is not associated with the presence of psychotic disorder. However, when severity is considered, a different picture emerges (see Tables 6.3-6.4). The majority of controls (78.5%) experienced events that were non-severe (i.e. rated as some or little/none, or rated as marked/moderate for the short-term only) or no events at all. Only around a fifth of controls (21.5%) experienced at least one severe event where the increased threat persisted (i.e. given a long-term rating of marked or moderate). This is in contrast to cases, where nearly half the group experienced events which carried a severe threat rating (cases 48.6%).

Taken together these findings suggest that exposure to severe events was associated with around a three-fold increased odds of psychosis (w.adj. OR 3.59, 95% CI 2.25-5.72, $p < 0.001$). Furthermore, there was evidence to suggest that exposure to an increasing number of severe events was associated with a cumulative increase in the odds of psychosis. As shown in Figure 6.1, exposure to one severe event was associated with over a two-fold increase in the odds of psychosis (w.adj. OR 2.87, 95% CI 1.62-5.08, $p < 0.001$), and exposure to at least two severe events was associated with an increase in the odds of psychosis by nearly five-fold (w.adj. OR 4.86, 95% CI 2.58-9.14, $p < 0.001$).

The association between severe life events and psychosis was also analysed in a restricted sample ($n=257$) of individuals who had completed the LEDS, CEQ and FIGS assessments, to see whether these effects held after controlling for additional confounders of current cannabis use and family history of psychosis (in addition to the *a priori* confounders). It is acknowledged that this will result in less precise estimates given the sample size (a loss of 297 subjects overall), but for consistency and completeness, analyses were conducted and are presented. In the adjusted model in this subsample, a similar effect was found and there was no evidence of confounding by these additional factors (w.adj. OR 5.79, 95% CI 2.41-13.92, $p < 0.001$).

6.3.3. Were more severe difficulties associated with case status?

Cases were far more likely to experience severe difficulties (i.e. those rated as marked or high moderate) compared with controls (cases 53.6% vs. controls 25.6%, $p < 0.001$). Exposure to at least one severe difficulty was associated with nearly a five-fold increased odds of psychosis (w.adj. OR 4.76, 95% CI 2.98-7.62, $p < 0.001$). As with the event severity, there was evidence to suggest that exposure to an increasing number of severe difficulties was associated with a cumulative increase in the odds of psychosis. As shown in Figure 6.2, exposure to one severe difficulty was associated with a three-fold increase in the odds of psychosis (w.adj. OR 3.09, 95% CI 1.85-5.18, $p < 0.001$) and exposure to at least two severe difficulties was associated with an increase of around ten-fold (w.adj. OR 10.40, 95% CI 4.91-22.02, $p < 0.001$).

To explore whether the effects of severe difficulties remained after controlling for the additional confounders (in addition to the *a priori* confounders), separate analyses were conducted in a smaller sample (see Table 6.4). A similar pattern was evident after adjusting for these additional factors and there was no substantial difference in odds (w.adj. OR 5.18, 95% CI 2.22-12.11, $p < 0.001$).

It seems, then, that it is life events and difficulties at a moderate or marked level of severity that are associated with psychosis. All subsequent analyses consequently compared exposure to no or non-moderate/marked events and difficulties with exposure to moderate/marked events and difficulties, in addition to further characteristics.

Table 6.3 Association between severity of life events, difficulties and psychotic disorder

	Cases (n=253)	Controls (n=301)					
	n (%)	n (w%)	χ^2 †	df †	p†	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Event severity							
No/non-severe event(s)	130 (51.4)	237 (78.5)	44.94	1	<0.001	1	1
>1 severe events	123 (48.6)	64 (21.5)				3.45 (2.30-5.15)***	3.59 (2.25-5.72)***
Difficulty severity							
No/non- severe difficulties	117 (46.3)	227 (74.4)	46.03	1	<0.001	1	1
>1 severe difficulties	136 (53.6)	74 (25.6)				3.38 (2.29-4.97)***	4.76 (2.98-7.62)***

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). df, degrees of freedom. †, calculated using weights. OR, odds ratio. CI, confidence interval. *p<0.05; **p<0.01; ***p<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

Table 6.4 Association between severity of life events, difficulties and psychotic disorder, adjusted for other potential confounders in the smaller subsample

	Cases (n=92)	Controls (n=165)					
	n (%)	n (w%)	χ^2 †	df †	p †	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Event severity							
No/non-severe event(s)	48 (52.2)	132 (79.5)	20.82	1	<0.001	1	1
>1 severe events	44 (47.8)	33 (20.5)				3.55 (1.95-6.46)***	5.79 (2.41-13.92)***
Difficulty severity							
No/non- severe difficulties	47 (51.1)	119 (72.4)	11.70	1	0.001	1	1
>1 severe difficulties	45 (48.9)	46 (27.7)				2.51 (1.42-4.41)**	5.18 (2.22-12.11)***

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). df, degrees of freedom. †, calculated using weights. OR, odds ratio. CI, confidence interval. * $p<0.05$; ** $p<0.01$; *** $p<0.001$. ‡, adjusted for age, gender, ethnicity, main subject social class, current cannabis use and family history of psychosis. (Percentages may not add up to 100 due to rounding).

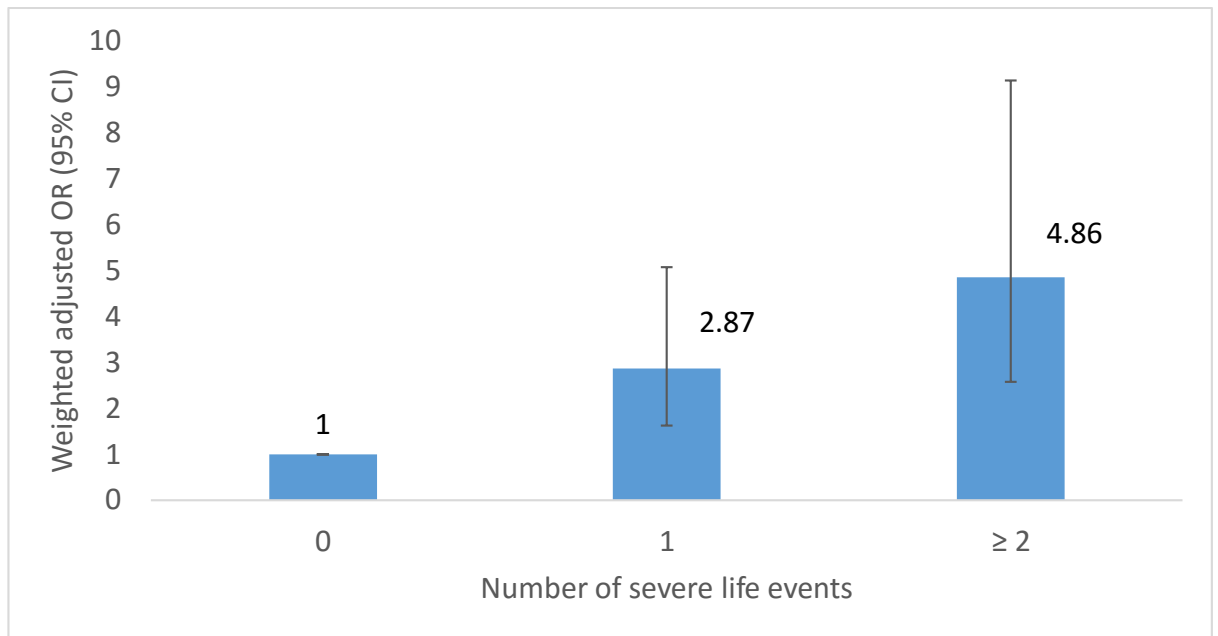


Figure 6.1 Cumulative severe life events and case-control status

Weighted odds ratio (OR) with 95% confidence intervals (CI), adjusted for age, gender, ethnicity, and main subject social class. Analyses were weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark.

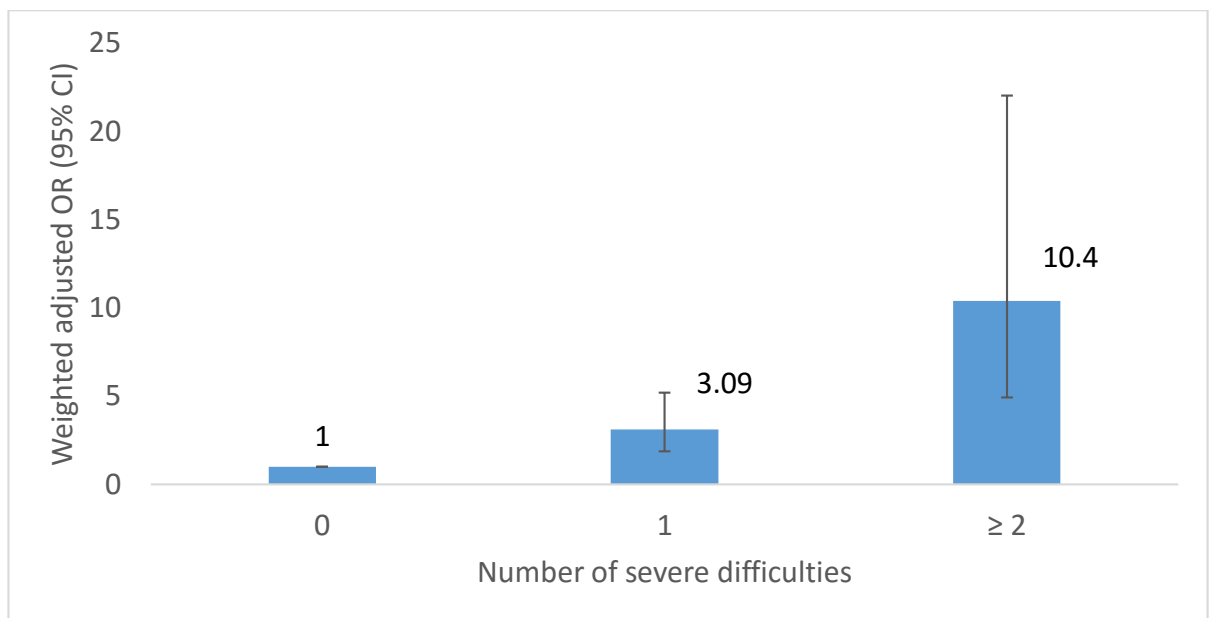


Figure 6.2 Cumulative severe difficulties and case-control status

Weighted odds ratio (OR) with 95% confidence intervals (CI), adjusted for age, gender, ethnicity, and main subject social class. Analyses were weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark.

6.3.4. Were severe events and difficulties associated with psychotic-like experiences in controls?

As highlighted in Chapter 2, exposure to life events may also be associated with an increased odds of PLE within general population samples and so it was hypothesised (hypothesis 1.3) that exposure to severe events and difficulties would be more prevalent amongst controls with PLE (n=38) compared with controls without PLE (n=263).

The main focus for these and subsequent PLE analyses was on comparing the controls with PLE to the controls without PLE. For completeness, associations between cases and controls without PLE and also a comparison of cases and controls with PLE was also shown. It is acknowledged that when comparing cases and non-PLE controls, any associations previously found in the main case-control sample, would likely become more pronounced by the removal of controls with PLE. However, the confidence intervals would inevitably widen due to the loss of power.

Tables 6.5-6.6 show the associations between severe events and difficulties and PLE. More controls with PLE experienced severe life events compared with controls without PLE, although exposure to severe life events was most prevalent amongst cases (cases 48.6% vs. controls with PLE 30.3% vs. controls without PLE 20.4%; $p < 0.001$). However, the association between exposure to severe life events and PLE status was modest and did not approach statistical significance (w.adj. OR 1.23, 95% CI 0.47-3.22); although these analyses could be underpowered due to the small numbers in the PLE group.

When looking at exposure to severe difficulties across the three groups, a stronger picture emerges. Controls with PLE were more likely to be exposed than controls without PLE and the prevalence of severe difficulties for the PLE group was similar to that reported by the psychosis cases (cases 53.6% vs. controls with PLE 48.5% vs. controls without PLE 22.8%; $p < 0.001$). Indeed, exposure to severe difficulties was associated with a three-fold increased odds of PLE amongst controls in this sample (w.adj. OR 3.80, 95% CI 1.64-8.79, $p = 0.002$). There did not appear to be a robust association between exposure to severe difficulties and psychotic disorder when the controls with PLE were used as the reference group (w.adj. OR 1.58, 95% CI 0.69-3.61, $p = 0.281$); providing further indication that controls with PLE reported similar levels of exposure as cases.

Table 6.5 Prevalence of severe life events and difficulties in psychosis cases, controls with and controls without PLE

	Cases (n=253)	Controls with PLE (n=38)	Controls without PLE (n=263)			
	n (%)	n (w%)	n (w%)	χ^2 †	df †	p†
Event severity						
No/non-severe event(s)	130 (51.4)	27 (69.7)	210 (79.6)	46.22	2	<0.001
>1 severe events	123 (48.6)	11 (30.3)	53 (20.4)			
Difficulty severity						
No/non-severe difficulties	117 (46.3)	21 (51.5)	206 (77.3)	54.22	2	<0.001
>1 severe difficulties	136 (53.6)	17 (48.5)	57 (22.8)			

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). df, degrees of freedom. PLE, psychotic-like experiences. †, calculated using weights. (Percentages may not add up to 100 due to rounding).

Table 6.6 Association between severe life events, difficulties and PLE status

	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Severe life events		
Psychosis cases vs. controls without PLE	3.68 (2.40-5.64)***	3.71 (2.29-6.02)***
Controls with PLE vs. controls without PLE	1.70 (0.72-4.00)	1.23 (0.47-3.22)
Psychosis cases vs. controls with PLE	2.17 (0.95-4.96)	3.01 (1.16-7.81)*
Severe difficulties		
Psychosis cases vs. controls without PLE	3.95 (2.61-5.96)***	5.99 (3.64-9.87)***
Controls with PLE vs. controls without PLE	3.22 (1.44-7.13)**	3.80 (1.64-8.79)**
Psychosis cases vs. controls with PLE	1.23 (0.57-2.67)	1.58 (0.69-3.61)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. OR, odds ratio. CI, confidence interval. PLE, psychotic-like experiences. *p<0.05; **p<0.01; ***p<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class.

6.3.5. Was the association between severe events, difficulties and psychosis moderated by gender?

Subsequent to examining main effects, the next step was to test the first part of hypothesis 1.4, and assess whether associations between severe life events, difficulties and psychosis were modified by gender and age, such that stronger effects would be found for women and younger participants.

Table 6.7 shows associations between severe life events, difficulties and psychosis stratified by gender, as well as the unadjusted and adjusted odds ratios for the association with case status. There was some evidence that the effect of severe life events on odds of psychosis was greater in men compared with women (OR for men 5.64, 95% CI 2.92-10.88, $p < 0.001$; OR for women 2.22, 95% CI 1.12-4.40, $p = 0.002$; p value for interaction term 0.055). In contrast, there was no evidence that gender modified the effect of severe difficulties on odds of psychosis.

6.3.6. Was the association between severe events, difficulties and psychosis moderated by age?

Table 6.8 shows the prevalence of severe life events and difficulties for cases and controls by two age groups: under 30 years and over 30 years, as well as the unadjusted and adjusted odds ratios for the association with case status, and the interaction term statistics used to assess the presence of an interaction with age. There was evidence that the effects of severe events varied by age. That is, the odds of psychosis after exposure to severe life events were six times higher in cases than controls among those under 30 years compared with two times for those over 30 years (OR for under 30 years 6.53, 95% CI 3.09-13.80, $p < 0.001$; OR for over 30 years 2.13, 95% CI 1.15-3.94, $p = 0.016$; p value for interaction term 0.024).

Table 6.8 also shows associations between severe difficulties and psychosis stratified by age. As with events, there was evidence that the effects of severe difficulties varied by age (p value for interaction term 0.016), such that the odds of psychosis after exposure to severe difficulties were around eight times higher in cases than controls among those under 30 years (w.adj. OR 8.65, 95% CI 4.28-17.47, $p < 0.001$), compared with two times for those above 30 years (w.adj. OR 2.75, 95% CI 1.48-5.12, $p = 0.001$).

Table 6.7 Association between severity of life events, difficulties and psychotic disorder, modified by gender

	Cases (n=253)	Controls (n=301)		
	n/N (%)	n/N (w%)	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Exposed to severe events				
Men	76/156 (48.7)	27/153 (16.9)	4.67 (2.67-8.17)***	5.64 (2.92-10.88)***
Women	47/97 (48.5)	37/148 (26.2)	2.65 (1.47-4.76)***	2.22 (1.12-4.40)*
			<i>p</i> value for interaction term=0.169	<i>p</i> value for interaction term=0.055
Exposed to severe difficulties				
Men	73/156 (46.8)	33/153 (21.9)	3.14 (1.85-5.35)***	4.13 (2.21-7.73)***
Women	63/97 (65.0)	41/148 (29.4)	4.45 (2.48-8.00)***	5.57 (2.78-11.16)***
			<i>p</i> value for interaction term=0.388	<i>p</i> value for interaction term=0.531

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). df, degrees of freedom. †, calculated using weights. OR, odds ratio. CI, confidence interval. **p*<0.05; ***p*<0.01; ****p*<0.001. ‡, adjusted for age, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

Table 6.8 Association between severity of life events, difficulties and psychotic disorder, modified by age at the time of assessment

	Cases (n=253)	Controls (n=301)		
	n/N (%)	n/N (w%)	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Exposed to severe events				
18-29 years	76/154 (49.4)	15/112 (11.8)	7.26 (3.69-14.29)***	6.53 (3.09-13.80)***
30-64 years	47/99 (47.5)	49/189 (25.9)	2.58 (1.50-4.44)***	2.13 (1.15-3.94)*
			<i>p</i> value for interaction term=0.020	<i>p</i> value for interaction term=0.024
Exposed to severe difficulties				
18-29 years	81/154 (52.6)	16/112 (13.7)	6.99 (3.61-13.53)***	8.65 (4.28-17.47)***
30-64 years	55/99 (55.6)	58/189 (31.0)	2.78 (1.64-4.72)***	2.75 (1.48-5.12)***
			<i>p</i> value for interaction term=0.033	<i>p</i> value for interaction term=0.016

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). df, degrees of freedom. †, calculated using weights. OR, odds ratio. CI, confidence interval. **p*<0.05; ***p*<0.01; ****p*<0.001. ‡, adjusted for gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

6.3.7. Were events and difficulties independent of illness?

After assessing the impact of severity, the next step was to see whether these effects held once the independence of events and difficulties were considered (see Table 6.9). The next section tests hypothesis 1.5, to see whether independent life events and difficulties would also be associated with an increased odds of psychosis.

If the experience of life events and difficulties were likely to be brought upon by the effects of potential (prodromal) illness characteristics, then we would be more likely to see an overrepresentation of possibly dependent events/difficulties in cases and no impact of independent events/difficulties on odds of psychosis. However, if events and difficulties which were outside of an individual's control were also likely to contribute to an increase in the odds of psychosis, then we would see individual effects for independent events/difficulties, alongside the effects of possibly dependent events/difficulties.

Of the subjects who experienced severe events, both cases and controls were most likely to report exposure to a combination of at least one independent and one possibly dependent event (cases 26.9% vs. controls 15.1%). However, we were unable to tell with this data whether the effects on case status were driven by the independent or possibly dependent events. As expected, exposure to events that were possibly dependent were more common in cases than controls (w.adj. OR 10.37, 95% CI 2.43-44.18, $p=0.002$), but exposure to events that were independent was also associated with an increased odds of psychotic disorder compared with exposure to no/non-severe events (w.adj. OR 3.09, 95% CI 1.08-8.81, $p<0.001$). This finding of an association between independent events and psychosis suggests that the association between life events and psychosis is not solely driven by characteristics of prodromal illness.

Similarly to events, exposure to difficulties which were possibly dependent was also associated with an increased odds of psychotic disorder, this time by around seven-fold (w.adj. OR 7.73, 95% CI 3.81-15.68, $p<0.001$), whereas exposure to difficulties which were independent was not associated with an increase in the odds of psychosis. Unlike for events, the effect of severe difficulties on odds of psychosis did not hold once independence was taken into consideration, such that the possibility that prodromal features drove some of these effects cannot be excluded.

Table 6.9 Association between independence of severe life events, difficulties and psychotic disorder

	Cases (n=253)	Controls (n=301)						
	n (%)	n (w%)	χ^2 †	df †	p†	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)	
Event independence								
No/non-severe event(s)	130 (51.4)	237 (78.5)	61.84	3	<0.001	1	1	
Severe independent event(s) only	12 (4.7)	14 (4.8)				1.50 (0.63-3.59)	3.09 (1.08-8.81)*	
Severe possibly dependent event(s) only	43 (17.0)	3 (1.6)				16.08 (3.39-76.29)***	10.37 (2.43-44.18)**	
Severe independent & possibly dependent event(s)	68 (26.9)	47 (15.1)				2.72 (1.73-4.27)***	2.73 (1.61-4.63)***	
Difficulty independence								
No/non-severe difficulties	117 (46.3)	227 (74.4)	62.03	3	<0.001	1	1	
Severe independent difficulties only	6 (2.4)	11 (3.4)				1.12 (0.40-3.16)	3.92 (0.63-24.38)	
Severe possibly dependent difficulties only	69 (27.3)	14 (6.0)				7.35 (3.66-14.78)***	7.73 (3.81-15.68)***	
Severe independent & possibly dependent difficulties	61 (24.1)	49 (16.2)				2.39 (1.50-3.80)***	3.59 (2.06-6.26)***	

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). df, degrees of freedom. †, calculated using weights. OR, odds ratio. CI, confidence interval. *p<0.05; **p<0.01; ***p<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

6.3.8. Were events and difficulties experienced by cases more likely to be subject focused?

As well as looking at the impact of severity and independence, another hypothesis this chapter sought to investigate was whether subject focused events and difficulties would be more common amongst cases than joint and other focused events/difficulties (hypothesis 1.6). Therefore, this next section assessed whether the odds of psychosis were higher in those who had experienced severe events and difficulties which were solely subject focused, compared with those who had been exposed to joint and other focused events and difficulties, or a combination of joint, other and subject focused events and difficulties.

It should be noted here that although Brown and Harris (1989b) have analysed subject focused events as a combination of solely subject focused and joint focused events, this thesis has taken the approach to analyse solely subject focused events and difficulties as their own category, and compare these to joint and other focused events/difficulties. It was felt that solely subject focused experiences would be more likely to show associations with psychosis, in keeping with the ideas of threat and intrusiveness, which potentially have a more damaging influence when experienced as an individual.

According to Brown and Harris (1989b), the focus scale is a critical element of the LEDS measure because only severe events (rated as '2-moderate' or '1-marked' on long-term threat) which were also focused on the subject have been associated with the onset of depression. Although this association has not been previously tested for psychosis, it seems plausible that it would also hold true for this disorder, as exposure to these experiences may create a feeling of being targeted and singled out.

As outlined in Table 6.10, cases were more likely to report exposure to severe subject focused events compared with controls (cases 9.9% vs. controls 2.9%), whereas cases and controls did not differ as greatly in their exposure to severe joint and other focused events (cases 8.3% vs. controls 5.6%). Exposure to severe subject focused events was associated with around a four-fold increased odds of psychotic disorder (w.adj. OR 4.46, 95% CI 1.41-14.10, $p=0.011$). Exposure to severe joint and other focused events, was also associated with an increased odds of psychotic disorder (w.adj. OR 2.85, 95% CI 1.17-6.96, $p=0.022$), although the effect is not as strong as for solely subject focused events. A larger proportion of both cases and controls were exposed to a

combination of severe joint, other and subject focused events, and as with the other categories, exposure to this combination was also associated with an increased odds of psychosis, but by not as much as for solely severe subject focused events (w.adj. OR 3.63, 95% CI 2.14-6.17, $p<0.001$). It is unlikely that exposure to just subject focused events was associated with increases in the odds of psychosis over and above the other categories as the confidence intervals overlap considerably. However, there is some tentative evidence to suggest that if the focus of the life event is solely on the individual, the odds of psychosis are higher than if the focus is diffuse, i.e. focused on others as well.

Similarly to events, cases were more likely to be exposed to severe subject focused difficulties (cases 14.2% vs. controls 3.8%), whereas the prevalence of severe joint and other focused difficulties were more similar across the two groups (cases 6.3% vs. controls 5.2%). Exposure to severe subject focused difficulties was associated with an increased odds of psychosis of around seven-fold (w.adj. OR 7.52, 95% CI 2.57-22.00, $p<0.001$). As with events, exposure to severe joint and other focused difficulties was also associated with an increased odds of psychosis (w.adj. OR 3.69, 95% CI 1.56-8.75, $p=0.003$), as was exposure to a combination of severe difficulties of different foci (w.adj. OR 4.36, 95% CI 2.57-7.40, $p<0.001$), but the effect is highest in those exposed to solely subject focused difficulties. However, as stated before, due to the confidence intervals for each category overlapping, it is difficult to determine whether there is a specificity for focus, although these findings are tentatively in the hypothesised direction.

Table 6.10 Association between the focus of life events, difficulties and psychotic disorder

	Cases (n=253)	Controls (n=301)					
	n (%)	n (w%)	χ^2 †	df †	p†	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Event focus							
No/non-severe event(s)	130 (51.4)	237 (78.5)	47.49	3	<0.001	1	1
Severe joint & other focused event(s) only	21 (8.3)	18 (5.6)				2.25 (1.12-4.53)*	2.85 (1.17-6.96)*
Severe subject focused event(s) only	25 (9.9)	4 (2.9)				5.15 (1.52-17.41)**	4.46 (1.41-14.10)**
Severe joint, other & subject focused event(s)	77 (30.4)	42 (13.0)				3.58 (2.27-5.64)***	3.63 (2.14-6.17)***
Difficulty focus							
No/non-severe difficulty	117 (46.3)	227 (74.4)	51.11	3	<0.001	1	1
Severe joint & other focused difficulties only	16 (6.3)	15 (5.2)				1.94 (0.90-4.22)	3.69 (1.56-8.75)**
Severe subject focused difficulties only	36 (14.2)	8 (3.8)				6.02 (2.42-14.95)***	7.52 (2.57-22.00)***
Severe joint, other & subject focused difficulties	84 (33.2)	51 (16.6)				3.22 (2.07-5.01)***	4.36 (2.57-7.40)***

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). df, degrees of freedom. †, calculated using weights. OR, odds ratio. CI, confidence interval. *p<0.05; **p<0.01; ***p<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

6.3.9. Were any particular types of events and difficulties more common in cases than controls?

For completeness of the life events and difficulties analysis, further elaboration on whether any particular types of severe events and difficulties were more common in cases than controls was next considered. It should be stressed that this particular descriptive section was not hypothesis driven and was intended as a precursor to a more extensive analysis of the characteristic of intrusiveness.

An important caveat to keep in mind when looking at the frequency of events and difficulties across the domains is that the individual types of events and difficulties may not give us the full picture of what is actually going on. As outlined in the Introduction, many different events and difficulties can fall under the umbrella of each type, e.g. “work” events can include going for a job interview, starting a new job, and also being fired from a job; and so it is best to think of these categories as overall domains, and then if certain types appear to be more common in cases than controls, to perhaps then consider whether there are any common themes across types, e.g. intrusiveness, that may be responsible for driving any positive effects.

Overall, cases experienced a greater number of severe events and difficulties across all type domains compared with controls (see Tables 6.11 and 6.12). The most common event types reported by cases included crime (reported by 14.6%) and health (reported by 12.3%). An example of a severe health event reported by a case is the subject being admitted to hospital with a failing liver due to drug and alcohol abuse and having to have a biopsy performed (long-term threat rating of moderate). An example of a severe crime event reported by a case is the subject being taken away to a detention centre for the first time and being prevented from taking medications for long-term health conditions (long-term threat rating of marked). For controls, the most common categories included health (reported by 8.2%) and death (reported by 4.8%). An example of a severe health event from the control sample is the subject’s nephew being hospitalised due to exposure to chemical substances at work (long-term threat rating of moderate). An example of a severe death event from the control sample is the subject’s very close aunt dying from cancer (long-term threat rating of marked).

In terms of difficulties, the most common types reported by cases included health (reported by 16.6%), other relationships (reported by 14.2%) and finances (reported by 13%). An example of a severe health difficulty from the case sample is the

subject caring for their father who has untreated schizophrenia (threat rating of high moderate). An example of a severe other relationship from the case sample is the subject being disowned by their entire family since revealing their homosexuality in 2010. The family have not changed their mind despite the subject's repeated attempts at contact (threat rating of low marked). An example of a severe finance difficulty from the case sample is the subject not receiving their student loan for over one year despite repeated attempts to get this rectified (threat rating of high moderate). For controls, the most common difficulties experienced included health (reported by 12.9%) and work (reported by 5.2%). An example of a severe health difficulty from the control sample is the subject recovering from a back operation, with continuing pain for a few months and being unable to work (threat rating of high moderate). An example of a severe work difficulty from the control sample is the subject having ongoing issues with a colleague at work which resulted in the subject receiving threatening emails on a daily basis over a period of a few months (threat rating of high moderate).

For some of the examples outlined above, it is clear that they share a similar feature which cuts across the type domain. As well as a high level of severity, some of these examples also share the element of intrusiveness, i.e. interference and/or attempted control of the participant by others. This is apparent in the health event (subject being hospitalised and having a liver biopsy), the crime event (subject being taken away to a detention centre), and the severe work difficulty (subject being harassed by a colleague) examples given above. The next part of this chapter will now move on to see whether exposure to the characteristic of intrusiveness is associated with an increased odds of psychosis.

Table 6.11 Number of cases and controls experiencing at least one severe life event across each type

	Cases (n=253)	Controls (n=301)
Event type	n (%)	n (w%)
Education	5 (2.0)	1 (0.3)
Work	21 (8.3)	8 (0.4)
Reproduction	10 (4.0)	4 (1.3)
Housing	14 (5.5)	3 (0.8)
Finance	2 (0.8)	2 (0.8)
Crime	37 (14.6)	7 (2.0)
Health	31 (12.3)	24 (8.2)
Marital	24 (9.5)	12 (4.1)
Other relationship	22 (8.7)	4 (0.9)
Miscellaneous	2 (0.8)	2 (0.7)
Death	23 (9.1)	17 (4.8)

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark).

Table 6.12 Number of cases and controls experiencing at least one severe difficulty across each type

	Cases (n=253)	Controls (n=301)
Difficulty type	n (%)	n (w%)
Education	6 (2.4)	4 (1.7)
Work	26 (10.3)	14 (5.2)
Reproduction	1 (0.4)	0 (0.0)
Housing	27 (10.7)	6 (2.1)
Finance	33 (13.0)	6 (2.0)
Crime	21 (8.3)	3 (0.7)
Health	42 (16.6)	38 (12.9)
Marital	20 (7.9)	9 (3.5)
Other relationship	36 (14.2)	10 (2.9)
Miscellaneous	4 (1.6)	0 (0.0)
Death	0 (0.0)	0 (0.0)

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark).

6.3.10. Were intrusive events and difficulties particularly associated with case status?

In the previous sections of this chapter, severe, and also subject-focused, life events and difficulties showed particularly strong associations with psychosis. It is possible that what many of these exposures share is an element of intrusiveness, given the suggestion that intrusive events may be specific to psychosis (Harris, 1987). This next section sought to test whether these types of experiences matter by testing the second part of hypothesis 1.2, and seeing whether the odds of psychotic disorder were highest in those who had experienced more intrusive life events and difficulties.

Table 6.13 presents the associations with psychosis for severe non-intrusive events/difficulties and for severe intrusive events/difficulties. Cases were more likely to be exposed to severe intrusive events in the one year prior to onset compared with controls (cases 24.1% vs. controls 4.5%). The effect of intrusive events was greater than the effect of non-intrusive events. That is, severe intrusive events were associated with a six-fold increased odds of psychosis (w.adj. OR 6.73, 95% CI 3.31-13.67, $p<0.001$), compared with a two-fold increased odds for severe but non-intrusive events (w.adj. OR 2.61, 95% CI 1.52-4.49, $p=0.001$).

To explore whether the effects of intrusive events remained after controlling for the additional confounders of current cannabis use and family history of psychosis (in addition to *a priori* confounders), separate analyses were conducted in a smaller sample (see Table 6.14). Strong support remained for an association between intrusive life events and psychosis after adjustment for the additional confounders (w.adj. OR 10.75, 95% CI 2.90-39.82, $p<0.001$).

Similar effects were also seen when looking at the intrusiveness of difficulties. Cases were more likely than controls to report exposure to an intrusive difficulty (cases 24.1% vs. controls 3.4%), and exposure to these types of difficulties was associated with increasing the odds of psychosis by around twelve-fold (w.adj. OR 12.93, 95% CI 5.24-31.90, $p<0.001$) (Table 6.13). A similar pattern was also found after adjusting for current cannabis use and family history of psychosis (w.adj. OR 12.29, 95% CI 3.29-45.83, $p<0.001$), with no evidence of confounding (see Table 6.14).

Table 6.13 Association between event and difficulty intrusiveness and psychotic disorder

	Cases (n=253)	Controls (n=301)					
	n (%)	n (w%)	χ^2 †	df †	p†	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Event intrusiveness							
No/non-severe event(s)	130 (51.4)	237 (78.5)	57.90	2	<0.001	1	1
Severe non-intrusive event(s)	62 (24.5)	50 (17.0)				2.19 (1.38-3.50)***	2.61 (1.52-4.49)***
Severe intrusive event(s)	61 (24.1)	14 (4.5)				8.13 (4.16-15.88)***	6.73 (3.31-13.67)***
Difficulty intrusiveness							
No/non-severe difficulty	117 (46.3)	227 (74.4)	66.23	2	<0.001	1	1
Severe non-intrusive difficulties	75 (29.6)	63 (22.2)				2.15 (1.39-3.30)***	3.24 (1.93-5.43)***
Severe intrusive difficulties	61 (24.1)	11 (3.4)				11.44 (5.59-23.42)***	12.93 (5.24-31.90)***

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). df, degrees of freedom. †, calculated using weights. OR, odds ratio. CI, confidence interval. *p<0.05; **p<0.01; ***p<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

Table 6.14 Association between event and difficulty intrusiveness and psychotic disorder, adjusted for other potential confounders in the smaller subsample

	Cases (n=92)	Controls (n=165)					
	n (%)	n (w%)	χ^2 †	df †	p†	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Event intrusiveness							
No/non-severe event(s)	48 (52.2)	132 (79.5)	25.07	2	<0.001	1	1
Severe non-intrusive event(s)	25 (27.2)	27 (16.0)				2.57 (1.30-5.09)**	4.28 (1.58-11.62)**
Severe intrusive event(s)	19 (20.7)	6 (4.4)				7.08 (2.54-19.71)***	10.75 (2.90-39.82)***
Difficulty intrusiveness							
No/non-severe difficulty	47 (51.1)	119 (72.4)	20.96	2	<0.001	1	1
Severe non-intrusive difficulties	22 (23.9)	35 (21.7)				1.56 (0.80-3.05)	3.02 (1.17-7.77)*
Severe intrusive difficulties	23 (25.0)	11 (6.0)				5.92 (2.57-13.63)***	12.29 (3.29-45.84)***

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). df, degrees of freedom. †, calculated using weights. OR, odds ratio. CI, confidence interval. *p<0.05; **p<0.01; ***p<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class, current cannabis use and family history of psychosis. (Percentages may not add up to 100 due to rounding).

6.3.11. Was the association between intrusiveness events, difficulties and psychosis moderated by gender and age?

After assessing whether intrusive experiences were associated with case status, the next step was to test the second part of hypothesis 1.4, and see whether associations between intrusive life events, difficulties and psychosis were modified by gender and age, such that stronger effects would be found for women and younger participants. Against what was hypothesised, there was no evidence to suggest that the effect of intrusive events varied by age or gender, although the study had limited power to detect any such interactions (see Tables 6.15 and 6.16). Similarly, the effect of intrusive difficulties did not vary by gender. There was a tentative suggestion that there may be a weak effect of age, whereby the odds of psychosis after exposure to intrusive difficulties were higher among those under 30 years. However, this result is tentative at best given that intrusive difficulties were only reported by one control participant under 30 years.

Table 6.15 Association between intrusiveness of life events, difficulties and psychotic disorder, modified by gender

	Cases (n=253)	Controls (n=301)		
	n/N (%)	n/N (w%)	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Exposed to intrusive events				
Men	43/156 (27.6)	8/153 (5.6)	8.05 (3.36-19.27)***	9.14 (3.89-21.47)***
Women	18/97 (18.6)	6/148 (3.5)	7.59 (2.68-21.53)***	4.15 (1.24-13.93)*
			<i>p</i> value for interaction term=0.933	<i>p</i> value for interaction term=0.298
Exposed to intrusive difficulties				
Men	33/156 (21.2)	6/153 (3.8)	8.17 (3.08-21.65)***	7.49 (2.23-25.13)***
Women	28/97 (28.9)	5/148 (3.0)	19.57 (6.80-56.31)***	23.58 (7.37-75.48)***
			<i>p</i> value for interaction term=0.234	<i>p</i> value for interaction term=0.181

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). df, degrees of freedom. †, calculated using weights. OR, odds ratio. CI, confidence interval. **p*<0.05; ***p*<0.01; ****p*<0.001. ‡, adjusted for age, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

Table 6.16 Association between intrusiveness of life events, difficulties and psychotic disorder, modified by age at the time of assessment

	Cases (n=253)	Controls (n=301)		
	n/N (%)	n/N (w%)	Weighted unadjusted OR (95% CI)	Weighted adjusted OR [‡] (95% CI)
Exposed to intrusive events				
18-29 years	37/154 (24.0)	5/112 (3.3)	12.55 (4.53-34.82)***	10.02 (3.02-31.35)***
30-64 years	24/99 (24.2)	9/189 (5.1)	6.75 (2.83-16.08)***	4.87 (1.79-11.26)***
			<i>p</i> value for interaction term=0.364	<i>p</i> value for interaction term=0.282
Exposed to intrusive difficulties				
18-29 years	35/154 (22.7)	1/112 (1.0)	42.95 (5.73-322.16)***	56.76 (8.26-390.09)***
30-64 years	26/99 (26.3)	10/189 (4.5)	9.09 (3.91-21.12)***	6.86 (2.35-20.04)***
			<i>p</i> value for interaction term=0.164	<i>p</i> value for interaction term=0.060

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). df, degrees of freedom. †, calculated using weights. OR, odds ratio. CI, confidence interval. **p*<0.05; ***p*<0.01; ****p*<0.001. ‡, adjusted for gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

6.3.12. Did events cluster in the period closest to onset?

Early life events research in relation to schizophrenia suggested that severe events may cluster in the period closest to onset, with researchers proposing this period of clustering to likely be between three months to three weeks prior to an individual's first episode of psychosis (e.g. Brown & Birley, 1968; Day et al., 1987; Al-Khani et al., 1986; Bebbington et al., 1993). With these suggestions in mind, the final main effects analyses sought to examine these ideas by testing hypothesis 1.7, and seeing whether the odds of psychosis were higher in those who had experienced severe events closest to onset (less than 3 months prior to onset), compared with events occurring in other time periods (3-6 months, 6-9 months and 9-12 months prior to the onset of psychosis).

Table 6.17 presents the overall number of events experienced per quarter for cases and controls, the overall range of events experienced per period, the number and percentage of cases and controls exposed to at least one event during each period, and the odds ratios for the association with psychosis. Overall, cases experienced the highest number of events in the final quarter closest to onset and showed a small decline in the number of events experienced with each consecutive quarter (final quarter: 85 events, third quarter: 54 events, second quarter: 46 events and first quarter: 43 events). In contrast, the overall number of events experienced by controls was distributed more randomly than for cases and there was no pattern of decline further away from the end of the LEDS period (final quarter: 18 events, third quarter: 25 events, second quarter: 17 events and first quarter: 43 events). In fact, for controls, they experienced the highest number of events in the first quarter furthest away from the interview date.

When looking at the final quarter (0-3 months pre-onset/interview), the odds of being a case increased by around three and a half times for every additional severe life event experienced (w.adj. OR 3.49, 95% CI 1.78-6.84, $p < 0.001$). The odds of being a case were slightly lower for the third quarter (3-6 months pre-onset/interview) (w.adj. OR 2.20, 95% CI 1.16-4.18, $p = 0.016$), but were roughly similar for the second quarter (6-9 months pre-onset/interview) (w.adj. OR 3.36, 95% CI 1.83-6.15, $p < 0.001$). These findings suggest that there is unlikely to be a specific effect of time in increasing the odds of psychosis, and due to overlapping confidence intervals, these three time periods are unlikely to differ from each other. However, interestingly, for the period furthest away from onset/interview (9-12 months pre-onset/interview), there were no significant differences between cases and controls, who experienced the same number of severe events across this period (w.adj. OR 1.06, 95% CI 0.57-1.98, $p = 0.851$). These findings

tentatively suggest that it is exposure to severe events occurring less than 9 months prior to onset which are more associated with increased odds of psychosis.

As an extension to the initial hypothesis driven analysis, and to see whether the key finding of the seminal Brown and Birley (1968) study was replicable in this sample, the next step was to explore whether severe events had an even greater clustering effect in the final three weeks prior to onset (see Table 6.18). Similarly to the Brown and Birley (1968) paper, there was evidence to suggest that cases experienced far more severe events than controls in the final three weeks prior to onset/interview (cases, n=29 (11.5%) and controls, n=2 (0.6%)). A large association with psychosis was found. However, the precision of this result is clearly limited by the small numbers (w.adj. OR 19.70, 95% CI 3.89-99.78, $p<0.001$).

Table 6.17 Association between the timing of severe life events and psychotic disorder

Event timing	Cases (n=253)		Controls (n=301)		Weighted unadjusted OR (95% CI)	Weighted adjusted OR [†] (95% CI)
	Overall no. of events per period (range)	n (%) exposed to 1+ event in period	Overall no. of events per period (weighted range)	n (w%) exposed to 1+ event in period		
Final quarter (0-3 months prior to onset/interview)	85 (0-4)	64 (25.3)	18 (0-2)	14 (4.9)	3.84 (2.03-7.27)***	3.49 (1.78-6.84)***
Third quarter (3-6 months prior to onset/interview)	54 (0-3)	43 (17.0)	25 (0-3)	21 (7.0)	2.12 (1.24-3.64)**	2.20 (1.16-4.18)*
Second quarter (6-9 months prior to onset/interview)	46 (0-2)	42 (16.0)	17 (0-2)	16 (5.9)	2.91 (1.55-5.43)***	3.36 (1.83-6.15)***
First quarter (9-12 months prior to onset/interview)	43 (0-3)	36 (14.2)	43 (0-3)	35 (10.6)	1.27 (0.84-1.90)	1.06 (0.57-1.98)

OR, odds ratio. CI, confidence interval. w, weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. *p<0.05; **p<0.01; ***p<0.001. † adjusted for age, gender, ethnicity, main subject social class.

Table 6.18 Association between event rate in the final three weeks prior to onset/interview and psychotic disorder

Event timing	Cases (n=253)		Controls (n=301)		Weighted unadjusted OR (95% CI)	Weighted adjusted OR [†] (95% CI)
	Overall no. of events per period (range)	n (%) exposed to 1+ event in period	Overall no. of events per period (weighted range)	n (w%) exposed to 1+ event in period		
3 weeks prior to onset/interview	32 (0-2)	29 (11.5)	2 (0-1)	2 (0.6)	20.58 (4.89-86.56)***	19.70 (3.89-99.78)***

OR, odds ratio. CI, confidence interval. w, weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. *p<0.05; **p<0.01; ***p<0.001. † adjusted for age, gender, ethnicity, main subject social class.

6.4. Exploratory analyses

The main effects hypotheses have now been investigated and this chapter will continue by considering some more exploratory analyses, including an exploration of the impact of intrusive events and difficulties on PLE, the impact of difficulty duration, and the impact of severe life events and difficulties on general psychopathology symptom severity.

6.4.1. Were intrusive events and difficulties associated with psychotic-like experiences in controls?

As very strong associations were found between intrusive experiences and psychosis, an exploration of whether these types of experiences were more common in controls with PLE compared with controls without PLE was considered to be an informative addition to the analyses. As associations were previously found between severity and PLE, it is plausible that effects could also be found for intrusiveness. Tables 6.19-6.20 show the associations between intrusive events and difficulties between cases, and controls with and without PLE.

A greater number of controls with PLE experienced intrusive life events compared with controls without PLE, although exposure to intrusive life events was most prevalent amongst cases (cases 24.1% vs. controls with PLE 11.0% vs. controls without PLE 3.7%; $p < 0.001$). However, when looking at the odds ratio for association between exposure to intrusive life events and PLE status, although it goes in the expected direction, the confidence intervals suggest the effect is imprecise due to lack of power (w.adj. OR 2.31, 95% CI 0.62-8.65).

When looking at exposure to intrusive difficulties across the three groups, a stronger picture emerges. Controls with PLE were more likely to be exposed than controls without PLE, although by not as much as that reported by the cases (cases 24.1% vs. controls with PLE 10.4% vs. controls without PLE 2.5%; $p < 0.001$). Exposure to intrusive difficulties was associated with around a six-fold increased odds of PLE (w.adj. OR 6.19, 95% CI 1.51-25.40, $p = 0.011$).

Table 6.19 Prevalence of intrusive life events and difficulties in psychosis cases, controls with and controls without PLE

	Cases (n=253)	Controls with PLE (n=38)	Controls without PLE (n=263)			
	n (%)	n (w%)	n (w%)	χ^2 †	df †	p†
Event intrusiveness						
No/non-severe event(s)	130 (51.4)	27 (69.7)	210 (79.6)	59.58	3	<0.001
Severe non-intrusive event(s)	62 (24.5)	7 (19.3)	43 (16.7)			
Severe intrusive event(s)	61 (24.1)	4 (11.0)	10 (3.7)			
Difficulty intrusiveness						
No/non-severe difficulty	117 (46.3)	21 (51.5)	206 (77.3)	74.45	3	<0.001
Severe non-intrusive difficulties	75 (29.6)	13 (38.2)	50 (20.2)			
Severe intrusive difficulties	61 (24.1)	4 (10.4)	7 (2.5)			

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). df, degrees of freedom. PLE, psychotic-like experiences. †, calculated using weights. (Percentages may not add up to 100 due to rounding).

Table 6.20 Association between intrusive life events, difficulties and PLE status

	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Event intrusiveness		
Psychosis cases vs. controls without PLE	10.05 (4.67-21.63)***	8.22 (3.76-17.97)***
Controls with PLE vs. controls without PLE	3.39 (0.88-13.07)	2.32 (0.62-8.65)
Psychosis cases vs. controls with PLE	2.96 (0.90-9.75)	3.55 (1.07-11.71)*
Difficulty intrusiveness		
Psychosis cases vs. controls without PLE	15.98 (6.73-37.95)***	18.93 (6.57-54.54)***
Controls with PLE vs. controls without PLE	6.16 (1.54-24.63)**	6.19 (1.51-25.40)**
Psychosis cases vs. controls with PLE	2.59 (0.81-8.33)	3.06 (0.89-10.54)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. OR, odds ratio. CI, confidence interval. PLE, psychotic-like experiences. *p<0.05; **p<0.01; ***p<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class.

6.4.2. Were more long-term difficulties associated with case status?

Another area which was considered important to add to the exploratory analyses section was to see whether exposure to a longer duration of difficulties was more strongly associated with psychosis. Researchers have previously suggested that individuals with schizophrenia are more likely to be adversely affected by chronic difficulties (Norman & Malla, 1993b), and so it seems plausible that the longer the individual is exposed to a severe difficulty, the higher the odds of psychosis will be.

Table 6.21 shows the number of cases and controls exposed to either difficulties of 1-6 months duration, 7-12 months duration, or a combination of shorter and longer difficulties, and their associations with case status. Severe difficulties which lasted longer than six months were strongly associated with psychotic disorder compared with exposure to no or non-severe difficulties (w.adj OR 8.45, 95% CI 4.00-17.83, $p < 0.001$). However, exposure to a shorter period of difficulties of between 1-6 months duration was also associated with increasing the odds of psychosis (w.adj OR 6.81, 95% CI 2.30-20.15, $p < 0.001$). Furthermore, the effect of duration is even more difficult to disentangle because the majority of cases and controls who were exposed to severe difficulties experienced a combination of difficulties with both shorter (1-6 months) and longer (7-12 months) durations (cases 25.7% vs. controls 15.4%) (Table 6.21), and so we cannot say with any certainty that associations with psychosis are more likely to be driven by difficulties of a longer duration, despite this making intuitive sense.

6.4.3. Was the experience of severe events and difficulties associated with an increase in symptom severity in cases?

In order to increase knowledge of the impact of specific social factors on psychopathology, another area that was considered important to explore was whether the experience of severe life events and difficulties was associated with an increase in symptom severity (general psychopathology symptoms, as measured by GAF scores).

It is thought that cases with a stress driven illness may have a very acute and severe initial episode, with lots of florid positive symptoms that then remit relatively quickly; whereas those with a neurodevelopmental driven illness may have a more insidious onset with fewer florid positive symptoms (e.g. Murray et al., 1992; van Os et al., 1998). It was therefore expected that cases with more severe events would have a

more severe presentation, compared with those who did not experience severe experiences prior to onset.

Table 6.22 shows the median GAF symptom scores and interquartile ranges for cases with and cases without exposure to severe events and difficulties one year prior to onset. The GAF scores were measured from 1-100 with lower scores indicating worse symptoms. It should be noted that only 171 cases completed both the LEDS and GAF assessments so there is a reduction in power for these analyses. Contrary to what was expected, there were no differences in the level of general symptom severity between cases who were and were not exposed to severe experiences prior to onset. All cases, regardless of severe event/difficulty exposure showed a median general psychopathology symptom score within the moderate range. However, it should be noted that it is not possible to tease out the contributions of positive and negative psychotic symptoms, or indeed, any type of symptoms phenomenology using the GAF, and so it is unclear whether different effects would be seen when looking at specific symptoms. With this in mind, future analyses are planned when data is available in order to look at differences in psychotic phenomenology in relation to life event and difficulty exposure.

Table 6.21 Association between the duration of difficulties and psychotic disorder

	Cases (n=253)	Controls (n=301)					
Difficulty duration	n (%)	n (w%)	χ^2 †	df †	p†	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
No/non-severe difficulty	117 (46.3)	227 (74.4)	48.82	3	<0.001	1	1
Severe difficulty 1-6 months duration only	23 (9.1)	8 (3.6)				4.02 (1.54-10.52)**	6.81 (2.30-20.15)***
Severe difficulty 7-12 months duration only	48 (19.0)	21 (6.6)				4.63 (2.56-8.36)***	8.45 (4.00-17.83)***
Both severe difficulties of 0-6 months and 7-12 months duration	65 (25.7)	45 (15.4)				2.69 (1.68-4.30)***	3.20 (1.86-5.52)***

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). df, degrees of freedom. †, calculated using weights. OR, odds ratio. CI, confidence interval. *p<0.05; **p<0.01; ***p<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class.

Table 6.22 Median GAF symptom score in psychosis cases exposed and not exposed to severe life events and difficulties

	GAF symptom score Median (IQR)	<i>z</i>	<i>df</i>	<i>p</i>
Events				
No severe events (n=83)	55 (38-65)	-0.64	170	0.521
Severe events (n=88)	55 (38-68)			
Difficulties				
No severe difficulties (n=80)	54 (36-66)	-0.70	170	0.485
Severe difficulties (n=91)	55 (40-65)			

z= Wilcoxon rank sum test. *df*, degrees of freedom. GAF, Global Assessment of Functioning scale. IQR, inter-quartile range.

6.5. Overview of findings

The original study hypotheses tested in this chapter are restated in Table 6.23, along with a concise summary of the relevant results and an indication of whether each hypothesis was supported or not. Of the seven hypotheses assessed in this chapter, two were fully supported by the evidence obtained, four were partially supported, and no confirmatory evidence was found for one hypothesis.

6.6. Summary of Chapter 6

In summary, experiencing a greater of number of events and difficulties at any level of severity was not associated with an increase in the odds of psychosis, as proposed by the initial hypothesis. Interestingly, it was only when the severity of the experiences was included in the analyses that hypothesised case-control differences were evident. Around a half of cases (48.6%) and a fifth of controls (21.5%) were exposed to severe life events in the one year period prior to onset/interview, around a three-fold difference (w.adj. OR 3.59, 95% CI 2.25-5.72, $p < 0.001$), with evidence of a cumulative increase in odds with increasing number of severe events experienced. Just over half of the case sample (53.6%) and about a quarter of controls (25.6%) were

exposed to severe difficulties. As with severe events, exposure to severe difficulties was associated with increasing the odds of psychosis by nearly five-fold (w.adj. OR 4.76, 95% CI 2.98-7.62, $p<0.001$). There was also evidence of a linear increase in odds from none to two or more experiences of severe difficulties. Exposure to severe life events was not significantly associated with an increase in the odds of PLE amongst controls but exposure to severe difficulties was associated with an increase in the odds of PLE in this control sample (w.adj. OR 3.80, 95% CI 1.64-8.79, $p=0.002$).

There was a possible weak effect of gender moderating the relationship between severe life events and psychosis, such that the effect was stronger in men than women. No gender effects were found for severe difficulties. More robust evidence was found for age, whereby the odds of psychosis following severe life events and difficulties were higher for those aged less than 30 years than those aged above 30 years.

As hypothesised, there was some evidence to suggest that exposure to independent life events was associated with psychosis (w.adj. OR 3.09, 95% CI 1.08-8.81, $p<0.001$). However, there were no effects found for independent difficulties. The investigation of focus also followed what was hypothesised as exposure to severe subject focused events (w.adj. OR 4.46, 95% CI 1.41-14.10, $p=0.011$) and difficulties (w.adj. OR 7.52, 95% CI 2.57-22.00, $p<0.001$) were associated with increased odds of psychosis, and were higher than the odds for severe joint and other focused events/difficulties and a combination of joint, other and subject focused events/difficulties.

Exposure to severe and intrusive life events was found to be strongly associated with psychosis (w.adj. OR 6.73, 95% CI 3.31-13.67, $p<0.001$), and showed even greater effects than for severe but non-intrusive events. There was also a greater influence of severe and intrusive difficulties on the odds of psychosis compared with similarly severe experiences that were non-intrusive (w.adj. OR 12.93, 95% CI 5.24-31.90, $p<0.001$). There were no significant interactions with gender nor with age at the time of assessment for associations between intrusive life events, difficulties and psychotic disorder.

The final hypothesis set out to investigate whether severe events were more likely to cluster in the period closest to onset for cases. Although cases reported the majority of events in the final quarter closest to onset, there was no robust evidence which suggested any significant differences between the final, third and second quarters

of the one year prior to onset/interview. There was a weak suggestion that cases were exposed to more severe events in the final three weeks prior to onset but these findings were limited by small numbers.

Exploratory analyses found no significant associations between intrusive life events and PLE status in controls, but there was some evidence to suggest that exposure to intrusive difficulties was associated with increased odds of PLE amongst controls (w.adj. OR 6.19, 95% CI 1.51-25.40, $p=0.011$). It remains unclear whether severe difficulties of a longer duration are more likely to be associated with an increase in psychosis, and there was no evidence to suggest that exposure to severe events and difficulties increases general symptom severity amongst cases at the time of interview.

This chapter has laid out the contexts of how life events and difficulties impact the onset of psychosis and psychotic-like experiences and the thesis will now move on to consider some potential social and psychological mechanisms that may have an influence on how these relationships came about in this sample. The next chapter will investigate whether exposure to severe life events and difficulties combine synergistically with low social class, and with negative schemas about the self and others to increase the odds of psychosis, and whether symptoms of depression and anxiety may mediate the association between severe experiences and psychosis.

Table 6.23 Summary of Chapter 6 findings in relation to the original study hypotheses

Hypothesis	Supported?	Specific results
<i>1.1. Recent life events and difficulties will be associated with increased odds of psychosis, independent of a priori confounders of age, gender, ethnicity, and social class</i>	No	<ul style="list-style-type: none">- Controls reported more life events and difficulties than cases- After adjustment, exposure to >2 life events was associated with lower odds of being a case***, exposure to difficulties was not associated with an increase or decrease in odds of psychosis
<i>1.2. The odds of psychotic disorder will be highest in those who have experienced more severe, more frequent, and more intrusive life events and difficulties</i>	Yes	<ul style="list-style-type: none">- Exposure to severe events was associated with increased odds of psychosis of around a three-fold*** and there was evidence of a cumulative increase in odds after exposure to an increasing number of severe events***- Exposure to severe difficulties was associated with increased odds of psychosis of nearly five-fold*** and there was also evidence of a cumulative increase in odds with increasing exposure to severe difficulties***- Intrusive events were associated with a six-fold increased odds of psychosis*** and intrusive difficulties were associated with a twelve-fold increased odds of disorder***
<i>1.3. The odds of psychotic-like experiences will be highest in those who have experienced more severe life events and difficulties</i>	Partial	<ul style="list-style-type: none">- There was no association between severe events and PLE status but exposure to severe difficulties was associated with around a three-fold increased odds of PLE**
<i>1.4. Associations between severe and intrusive life events, difficulties and psychosis will be modified by gender and age, such that stronger effects will be found for women and younger participants</i>	Partial	<ul style="list-style-type: none">- The odds ratio for the association between severe life events and psychosis was higher in men than women*, but no gender effects were found for severe difficulties- The odds ratios for the association between severe life events, difficulties and psychosis were higher in those <30 years than those >30 years*- No effects of age or gender found for intrusive events and difficulties
<i>1.5. Independent life events and difficulties will also be associated with an increased odds of psychosis</i>	Partial	<ul style="list-style-type: none">- Exposure to independent life events was associated with a three-fold increased odds of psychosis***

Hypothesis	Supported?	Specific results
		- No association between independent difficulties and psychosis
1.6. <i>The odds of psychosis will be higher in those who have experienced severe events and difficulties which are solely subject focused, compared with exposure to joint and other focused events and difficulties</i>	Yes	- Odds of psychosis after exposure to subject focused events was higher than for other types of focus** and a similar pattern was found for subject focused difficulties***
1.7. <i>The odds of psychosis will be higher in those who have experienced severe life events closest to onset (less than 3 months prior to onset), compared with events occurring at other time points (3-6 months, 6-9 months and 9-12 months prior to the onset of psychosis).</i>	Partial	- Cases reported the majority of events in the final quarter closest to onset but similar increases in odds of psychosis were seen across the final, third and second quarter - There was a weak suggestion that cases were exposed to more severe events in the final three weeks prior to onset but these findings were limited by small numbers***

*p<0.05; **p<0.01; ***p<0.001.

CHAPTER 7 - Life Events & Psychosis: Mechanisms

Synopsis

Cognitive models of psychosis suggest that exposure to severe life events and difficulties in adulthood may, for some individuals, reactivate negative core schemas about the self and others which were developed earlier in life. These negative beliefs have been shown to be more common among both those with psychotic disorder and psychotic experiences in the general population. Negative core schemas may have a synergistic effect on the relationship between severe life events and difficulties, whereby the effect of adult adversity combines with (or depends on) negative schemas to increase the risk of psychosis. Further evidence also suggests that affective symptoms (including depression and anxiety), adversity and psychosis are very much interlinked and it may be that depression and anxiety lie on a causal path between life events and psychosis. Although the potential synergistic and mediating effects of negative schemas and affective processes are theoretically supported, no research has yet been published which has assessed these variables in pathways between severe adult life events/difficulties and the onset of psychosis.

Furthermore, although research also implicates social class as a key demographic correlate of stressful experiences, very little research has considered the impact of social class on the association between life events, difficulties and psychosis. Therefore, to follow on from the analyses of the main effects of life events and difficulties on the odds of psychosis, the potential synergistic effects of both low social class and negative schemas on the association between severe events, difficulties and psychosis, and also the potential mediation effects of affective processes, were explored in this chapter.

7.1. Hypotheses

Schemas:

2.1. Cases will report higher levels of negative schematic beliefs about the self and about others compared with controls;

2.2. Controls with PLE will report higher levels of negative schematic beliefs about the self and about others compared with controls without PLE;

Social and Psychological Synergistic Effects:

3.1. Severe life events and difficulties will combine synergistically with lower social class status to increase the odds of psychotic disorder beyond the effects of each alone;

3.2. Life events and difficulties will combine synergistically with a) negative schematic beliefs about the self and b) negative schematic beliefs about others, to increase odds of both psychotic disorder and PLE, beyond the effects of each alone.

Affective Symptoms and Mediation:

4.1. Cases will report greater levels of anxiety and depression compared with controls;

4.2. Controls with PLE will report greater levels of anxiety and depression compared with controls without PLE;

4.3. The association between recent life events, difficulties and psychosis (both clinical disorder and psychotic experiences in the control sample) will be mediated by a) higher levels of depression and b) higher levels of anxiety.

7.2. Analysis plan

All analyses in this chapter were weighted (see Methods chapter for further details of the weighting procedure), unless otherwise stated. Due to a non-normal distribution for the negative and positive core schema scores, and also the anxiety and depression scores, the median values and interquartile range (IQR) were presented. In order to explore associations between schemas, affective symptoms and psychosis, the continuous schema scores (scored from 0-24) and the anxiety (scored from 0-56) and depression scores (scored from 0-54) were recoded to form binary variables. The total sample median was assessed and median splits were used to dichotomise total scores for negative self (1 or more = present) and negative other (3 or more = present), positive self (13 or more = present) and positive other (12 or more = present), anxiety symptoms (5 or more = present) and depression symptoms (4 or more = present). Using the overall sample median-split may restrict the comparisons as different cut points

exist for cases and controls, however, this is in line with previous research studies (e.g. Fisher et al., 2012).

Logistic regression was used to assess the associations between the psychological variables and case-control status, and multinomial logistic regression was used to assess the associations between the psychological variables and PLE status. These analyses were firstly conducted unadjusted and then adjusted for *a priori* confounders of age, gender, ethnicity, and social class.

Where power allowed (i.e. for analyses of schemas, affective symptoms and both case-control status and PLE status), analyses were also repeated after adjusting for additional confounders of current cannabis use and family history of psychosis. It is acknowledged that including these additional confounders will result in less precise estimates given the sample size, but for consistency and completeness, analyses were conducted and presented. These additionally adjusted models are presented separately as data was only available for a subset of participants with completed assessments.

To examine whether exposure to severe life events and difficulties combined synergistically with lower social class status to increase the odds of psychotic disorder, interaction contrast ratios (ICRs) were used to test for interaction on an additive scale (i.e., departure from additivity), and evidence of a potential interaction was indicated by an ICR of greater than zero. To examine whether exposure to severe life events and difficulties combined synergistically with negative schemas about the self and others to increase the risk of psychotic disorder and PLE in controls, ICRs were also used to test for interaction on an additive scale. A more liberal approach was taken to *p* values when analysing synergistic effects because these are more difficult to detect. This was to ensure that no potential synergistic effects were missed. However, it is noted that although this approach aims to avoid type II errors, minimising the risk of these errors increases the risk of type I errors, so with this in mind, any effects where $p > 0.05$ were cautiously reported.

The life events and difficulties variable which was used for these analyses was a binary severity variable: any severe life event vs. no severe life event. Although severe and intrusive experiences showed even stronger associations with case status, the numbers exposed become too small to include in these further analyses. The dichotomised variables for negative self and other schemas (cut at the median) were also used in these analyses. The synergistic effects analyses were completed for cases vs. controls and for controls with PLE vs. controls without PLE.

The potential mediating effect of affective symptoms, i.e. levels of depression and anxiety, were assessed using the `binary_mediation` command in Stata. These analyses were conducted using the dichotomised severe life event and difficulties variables and the dichotomised variables for anxiety and depression levels (cut at the median). The mediation analyses were completed for cases vs. controls and for controls with PLE vs. controls without PLE. Standardised coefficients were reported for the indirect effects of anxiety and depression, the direct effects, and the total effects, along with their 95% confidence intervals. These were calculated using the bootstrap command with 500 bootstrap replications, and the bias-corrected confidence intervals were reported. These mediation analyses were unable to be weighted.

The synergistic effects and mediation analyses were only adjusted for *a priori* confounders, and not the additional confounders of current cannabis use and family history of psychosis. This was decided because interaction effects are difficult to detect, usually due to limited power, and thus the substantial loss of participants for these additional measures was likely to make any effects even harder to detect, i.e. missing data for a maximum of 229 subjects (dropping from a total of 474 to 245 participants).

All analyses were conducted using Stata 11.2.

7.3. Introduction to the psychological mechanisms sample

When moving on from considering the main effects of life events and difficulties on psychosis, to a consideration of potential mediation and synergistic effects, the sample size becomes more restricted due to missing data on the psychological assessments.

This chapter will firstly explore the influence of positive and negative schemas, where the sample size of participants with complete LEDS and BCSS assessments is 492 subjects (203 cases and 289 controls). The chapter will then move on to consider the role of affective processes, and the number of subjects with complete LEDS data and HAM-A anxiety questionnaires is 493 subjects (206 cases and 287 controls). The sample size with complete LEDS data and HAM-D depression questionnaires is smaller at 474 subjects (187 cases and 287 controls). The number of subjects with complete LEDS data and both the affective symptom questionnaires drops to 471 subjects (184

cases and 287 controls). For the PLE comparisons, the number of controls with PLE who also have complete LEDS and psychological data drops by three participants to a total of 35 subjects.

The samples used for the analyses in this chapter (i.e. total sample of participants with complete LEDS, BCSS, HAM-A and HAM-D, $n=465$) were checked for their basic demographics, i.e. age, gender, ethnicity and main subject social class, to see whether there were any differences compared with those who had dropped out for these analyses, i.e. participants who had completed the LEDS, and were therefore present in the main effect analyses, but had not completed these further psychological questionnaires ($n=48$). Assessment completers and drop-outs did not significantly differ with regard to age, gender and ethnicity (see Table 7.1). However, there were some differences with regard to social class and the participants included in the analysis were more likely to be of a higher social class status than those who dropped out before completing these measures ($p=0.041$). For the most part, these samples were broadly comparable with regard to sociodemographic characteristics.

Table 7.1 Comparison of socio-demographic characteristics between completers and drop-outs

	Completers (n=465)	Drop-outs (n=48)	<i>t</i> *	df*	<i>p</i> *
	Weighted Mean (SD)	Weighted Mean (SD)			
Age in years	33.47 (11.80)	34.15 (9.46)	0.45	512	0.651
	n (w%)	n (w%)	χ^2 *	df*	p*
Sex					
Male	257 (54.6)	20 (44.7)	1.72	1	0.207
Female	208 (45.4)	28 (55.3)			
Ethnicity					
White British	173 (36.3)	12 (26.3)	6.37	5	0.298
White Other	51 (15.5)	12 (27.8)			
Black African	95 (18.5)	9 (16.9)			
Black Caribbean	78 (14.8)	8 (15.2)			
Asian (all)	19 (5.0)	4 (7.5)			
Other	49 (10.0)	3 (6.4)			
Subject social class (main)					
Salariat	163 (37.3)	11 (22.5)	11.93	5	0.041
Intermediate	120 (25.9)	15 (32.1)			
Working Class	105 (21.9)	17 (34.7)			
Student	49 (8.8)	0 (0.0)			
Long-term unemployed	17 (3.6)	3 (6.4)			
Non-classifiable	11 (2.5)	2 (4.3)			

df, degrees of freedom. SD, standard deviation. w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). *, calculated using weights. Figures in bold indicate $p < 0.05$. (Percentages may not add up to 100 due to rounding).

7.4. Schemas

7.4.1. Negative schemas and case-control status

In order to address hypothesis 2.1, the first step was to determine whether cases reported higher levels of negative schematic beliefs about the self and about others compared with controls. The results are presented in Tables 7.2 and 7.3.

Cases reported higher negative self-schema scores compared with controls (case median: 2 (IQR: 0-6) vs. weighted control median: 0 (IQR: 0-2)), see Table 7.2. After controlling for *a priori* confounders, there was evidence to suggest that having greater negative self-schemas (cut at the median) was associated with increased odds of being a case (w.adj. OR 3.17, 95% CI 1.97-5.11, $p < 0.001$) (Table 7.3).

A similar pattern was evident for negative schemas about others, whereby cases reported a higher negative other-schema score compared with controls (case median: 5 (IQR: 1-11) vs. weighted control median: 1 (IQR: 0-6)), see Table 7.2, and an increased level of negative other-schemas (cut at the median) was associated with increased odds of psychosis (w.adj. OR 1.96, 95% CI 1.23-3.12, $p = 0.005$) (Table 7.3).

Table 7.2 Median negative schema scores in cases and controls

	Cases (n=203)	Controls (n=289)
	Median (IQR)	Weighted Median (IQR)
Negative self-schema	2 (0-6)	0 (0-2)
Negative other-schema	5 (1-11)	1 (0-6)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. IQR, inter-quartile range.

Table 7.3 Association between negative schemas and psychotic disorder

	Cases (n=203)	Controls (n=289)					
	n (%)	n (w%)	χ^2 †	df †	p †	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Negative self-schema							
Low (0)	72 (35.5)	180 (59.9)	28.55	1	<0.001	1	1
High (1-24)	131 (64.5)	109 (40.1)				2.71 (1.82-4.04)***	3.17 (1.97-5.11)***
Negative other-schema							
Low (0-2)	70 (34.5)	166 (58.8)	28.46	1	<0.001	1	1
High (3-24)	133 (65.5)	123 (41.2)				2.72 (1.83-4.03)***	1.96 (1.23-3.12)**

w, weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. † calculated using weights. df, degrees of freedom. OR, odds ratio. CI, confidence interval. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. ‡ adjusted for age, gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

Table 7.4 displays the median negative schema scores for the restricted sample (n=250) of subjects who had completed the LEDS, BCSS, CEQ and FIGS assessments, and Table 7.5 shows the adjusted models controlling for both *a priori* confounders and current cannabis use and a family history of psychosis. As seen above, there was strong evidence of an association between high negative self-schemas and increased odds of psychosis (w.adj. OR 2.97, 95% CI 1.43-6.19, p=0.004). However, following adjustment for cannabis use and family history of psychosis, the effect for negative other-schemas was attenuated and no longer significant at the conventional 5% level (w.adj. OR 1.45, 95% CI 0.67-3.10, p=0.342). Family history was primarily responsible for this attenuation.

Table 7.4 Median negative schema scores in cases and controls, adjusted for other potential confounders in the smaller subsample

	Cases (n=85)	Controls (n=165)
	Median (IQR)	Weighted Median (IQR)
Negative self-schema	2 (0-4)	0 (0-2)
Negative other-schema	6 (1-11)	2 (0-6)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. IQR, inter-quartile range.

Table 7.5 Association between negative schemas and psychosis, adjusted for other potential confounders in the smaller subsample

	Cases (n=85)	Controls (n=165)					
	n (%)	n (w%)	χ^2 †	df †	p†	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Negative self-schema							
Low (0)	28 (32.9)	97 (55.4)	11.38	1	0.002	1	1
High (1-24)	57 (67.1)	68 (44.6)				2.53 (1.41-4.55)***	2.97 (1.43-6.19)**
Negative other-schema							
Low (0-2)	30 (35.3)	87 (54.9)	8.62	1	0.006	1	1
High (3-24)	55 (64.7)	78 (45.1)				2.23 (1.25-3.96)**	1.45 (0.67-3.10)

w, weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. † calculated using weights. df, degrees of freedom. OR, odds ratio. CI, confidence interval. *p<0.05; **p<0.01; ***p<0.001. ‡ adjusted for age, gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

7.4.2. Negative schemas and PLE status

In order to address hypothesis 2.2, the next section assessed whether controls with PLE reported higher levels of negative schematic beliefs about the self and about others compared with controls without PLE.

Tables 7.6-7.9 show the associations between negative schemas and psychosis in cases, and controls with and without PLE. Interestingly, the median negative self-schema score was the same for both cases and controls with PLE, although the IQR was larger for cases. Controls without PLE had the lowest level of negative self-schemas (case median: 2 (IQR: 0-6) vs. weighted control with PLE median: 2 (IQR: 0-4) vs. weighted control without PLE median: 0 (IQR: 0-1)), see Table 7.6. As well as being associated with an increased odds of psychotic disorder, an increased level of negative self-schemas was also associated with an increased odds of PLE in this sample (w.adj. OR 3.11, 95% CI 1.31-7.35, $p=0.010$) (Table 7.7).

When looking at the negative other-schema scores across cases, and controls with and without PLE, a similar pattern was apparent. Controls with PLE had far higher negative other-schema scores than controls without PLE, and actually a little higher than the case subjects (case median: 5 (IQR: 1-11) vs. weighted control with PLE median: 7 (IQR: 1-12) vs. weighted control without PLE median: 1 (IQR: 0-6)), see Table 7.6. When controls without PLE were used as the reference group, there was evidence that an increase in negative other-schemas was associated with both psychotic disorder (w.adj. OR 2.28, 95% CI 1.41-3.70, $p=0.005$) and PLE amongst controls (w.adj. OR 3.77, 95% CI 1.48-9.59, $p=0.005$) (Table 7.7).

Table 7.6 Negative schemas in psychosis cases, controls with and controls without PLE

	Cases (n=203)	Controls with PLE (n=35)	Controls without PLE (n=254)
	Median (IQR)	Weighted Median (IQR)	Weighted Median (IQR)
Negative self-schema	2 (0-6)	2 (0-4)	0 (0-1)
Negative other-schema	5 (1-11)	7 (1-12)	1 (0-6)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. IQR, inter-quartile range. PLE, psychotic-like experiences.

Table 7.7 Association between negative schemas and PLE status

	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Negative self-schemas		
Psychosis cases vs. controls without PLE	3.06 (2.02-4.64)***	3.71 (2.22-6.18)***
Controls with PLE vs. controls without PLE	3.08 (1.37-6.93)**	3.11 (1.31-7.35)**
Psychosis cases vs. controls with PLE	1.00 (0.44-2.23)	1.19 (0.51-2.77)
Negative other-schemas		
Psychosis cases vs. controls without PLE	3.14 (2.08-4.73)***	2.28 (1.41-3.70)***
Controls with PLE vs. controls without PLE	3.96 (1.60-9.80)**	3.77 (1.48-9.59)**
Psychosis cases vs. controls with PLE	0.79 (0.32-1.97)	0.61 (0.23-1.56)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. OR, odds ratio. CI, confidence interval. PLE, psychotic-like experiences. *p<0.05; **p<0.01; ***p<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class.

When looking at the subsample of participants with cannabis and family history data, the cases and controls with PLE continued to have higher scores for negative self-schemas compared with controls without PLE (case median: 2 (IQR: 0-4) vs. weighted control with PLE median: 2 (IQR: 1-7) vs. weighted control without PLE median: 0 (IQR: 0-2)), see Table 7.8. There also continued to be support for an association between increased levels of negative self-schemas and both psychotic disorder (w.adj. OR 4.29, 95% CI 1.93-9.55, $p < 0.001$) and PLE in controls (w.adj. OR 7.15, 95% CI 2.26-22.69, $p = 0.001$), after adjustment for the additional factors of current cannabis use and family history of psychosis (see Table 7.9).

Cases and controls with PLE also continued to have higher scores for negative other-schemas compared with controls without PLE (case median: 6 (IQR: 1-11) vs. weighted control with PLE median: 6 (IQR: 1-11) vs. weighted control without PLE median: 2 (IQR: 0-5)), see Table 7.8. Following this additional adjustment, the association between negative other-schemas and psychosis was attenuated and there was no longer a significant association with psychotic disorder (w.adj. OR 1.75, 95% CI 0.80-3.83, $p = 0.161$), but there remained to be an association with PLE status (w.adj. OR 3.18, 95% CI 1.00-10.13, $p = 0.050$) (see Table 7.9).

Table 7.8 Negative schemas in psychosis cases, controls with and controls without PLE within the restricted subsample

	Cases (n=85)	Controls with PLE (n=25)	Controls without PLE (n=140)
	Median (IQR)	Weighted Median (IQR)	Weighted Median (IQR)
Negative self-schema	2 (0-4)	2 (1-7)	0 (0-2)
Negative other-schema	6 (1-11)	6 (1-11)	2 (0-5)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. IQR, inter-quartile range. PLE, psychotic-like experiences.

Table 7.9 Association between negative schemas and PLE status, adjusted for other potential confounders in the smaller subsample

	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Negative self-schemas		
Psychosis cases vs. controls without PLE	3.20 (1.73-5.92)***	4.29 (1.93-9.55)***
Controls with PLE vs. controls without PLE	7.03 (2.35-21.02)***	7.15 (2.26-22.69)***
Psychosis cases vs. controls with PLE	0.45 (0.15-1.38)	0.60 (0.18-2.05)
Negative other-schemas		
Psychosis cases vs. controls without PLE	3.57 (1.19-10.69)*	1.75 (0.80-3.83)
Controls with PLE vs. controls without PLE	2.63 (1.45-4.76)**	3.18 (1.00-10.13)*
Psychosis cases vs. controls with PLE	0.74 (0.24-2.25)	0.54 (0.16-1.85)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. OR, odds ratio. CI, confidence interval. PLE, psychotic-like experiences. *p<0.05; **p<0.01; ***p<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class, current cannabis use and family history of psychosis.

7.4.3. Positive schemas and case-control status

As shown in Table 7.10, it appears that cases and controls differed in their level of positive self-schemas (case median: 13 (IQR: 7-17) vs. weighted control median: 14 (IQR: 10-17)). However, following adjustment for *a priori* confounders, there was no association found between positive self-schemas (cut at the median) and case status (w.adj. OR 0.90, 95% CI 0.56-1.43, $p=0.655$) (Table 7.11).

Controls were found to have higher levels of positive other-schemas compared with cases (case median: 11 (IQR: 7-15) vs. weighted control median: 13 (IQR: 10-16)), see Table 7.10. When *a priori* confounders were taken account of, there was a small indication that increased levels of positive other-schemas (cut at the median) was associated with lower odds of psychosis; however this result did not quite reach standard significance levels (w.adj. OR 0.67, 95% CI 0.42-1.06, $p=0.087$) (Table 7.11).

Table 7.10 Median positive schema scores in cases and controls

	Cases (n=203)	Controls (n=289)
	Median (IQR)	Weighted Median (IQR)
Positive self-schema	13 (7-17)	14 (10-17)
Positive other-schema	11 (7-15)	13 (10-16)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. IQR, inter-quartile range.

Table 7.11 Association between positive schemas and psychotic disorder

	Cases (n=203)	Controls (n=289)					
	n (%)	n (w%)	χ^2 †	df †	p†	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Positive self-schema							
Low (0-12)	97 (47.8)	125 (42.9)	1.15	1	0.313	1	1
High (13-24)	106 (52.2)	164 (57.1)				0.82 (0.56-1.21)	0.90 (0.56-1.43)
Positive other-schema							
Low (0-11)	105 (51.7)	107 (35.1)	13.64	1	<0.001	1	1
High (12-24)	98 (48.3)	182 (64.9)				0.50 (0.34-0.74)***	0.67 (0.42-1.06)

w, weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. † calculated using weights. df, degrees of freedom. OR, odds ratio. CI, confidence interval. *p<0.05; **p<0.01; ***p<0.001. ‡ adjusted for age, gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

To explore whether the effects of positive schemas remained the same after controlling for the additional confounders of current cannabis use and family history of psychosis (in addition to the *a priori* confounders), separate analyses were conducted in a smaller sample (see Table 7.13). A similar pattern was seen after adjusting for these additional factors and there was no substantial difference in odds when considering positive self-schemas, with no robust associations found with case status (w.adj. OR 1.11, 95% CI 0.53-2.34, $p=0.784$). There was also no evidence that positive other-schemas were associated with case status after additional adjustment (w.adj. OR 1.54, 95% CI 0.70-3.37, $p=0.281$).

Table 7.12 Median positive schema scores in cases and controls, adjusted for other potential confounders in the smaller subsample

	Cases (n=85)	Controls (n=165)
	Median (IQR)	Weighted Median (IQR)
Positive self-schema	13 (8-16)	14 (10-17)
Positive other-schema	11 (7-15)	12 (10-16)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. IQR, inter-quartile range.

Table 7.13 Association between positive schemas and psychosis, adjusted for other potential confounders in the smaller subsample

	Cases (n=85)	Controls (n=165)					
	n (%)	n (w%)	χ^2 †	df †	p†	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Positive self-schema							
Low (0-12)	39 (45.9)	68 (41.4)	0.47	1	0.519	1	1
High (13-24)	46 (54.1)	97 (58.7)				0.83 (0.47-1.46)	1.11 (0.53-2.34)
Positive other-schema							
Low (0-11)	44 (51.8)	69 (39.4)	3.50	1	0.078	1	1
High (12-24)	41 (48.2)	96 (60.6)				0.61 (0.35-1.07)	1.54 (0.70-3.37)

w, weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. † calculated using weights. df, degrees of freedom. OR, odds ratio. CI, confidence interval. *p<0.05; **p<0.01; ***p<0.001. ‡ adjusted for age, gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

7.4.4. Positive schemas and PLE status

Tables 7.14-7.17 show the associations between positive schemas and psychosis in cases, and controls with and without PLE. As was seen previously when the control sample was examined as a whole, there were not any substantial differences in the level of positive self-schemas between the cases, controls with PLE and controls without PLE in this sample (case median: 13 (IQR: 7-17) vs. weighted control with PLE median: 13 (IQR: 7-17) vs. weighted control without PLE median: 14 (IQR: 10-17)), see Table 7.14. Positive self-schemas were not associated with case or PLE status (Table 7.15). These findings also held after adjusting for additional confounders (see Tables 7.16 and 7.17).

When looking at the positive other-schemas scores across cases, and controls with and without PLE, a different pattern is seen. Controls with PLE had lower positive other-schema scores than controls without PLE, and showed similar median scores to the case subjects (case median: 11 (IQR: 7-15) vs. weighted control with PLE median: 11 (IQR: 6-16) vs. weighted control without PLE median: 13 (IQR: 10-16)), see Table 7.14. Interestingly, when the control group was separated in two according to PLE status, there was a stronger effect of positive other-schemas than when the case-control sample was analysed as a whole. Increased levels of positive other-schemas was associated with both lower odds of psychotic disorder (w.adj. OR 0.59, 95% CI 0.36-0.97, $p=0.036$), and of PLE (w.adj. OR 0.42, 95% CI 0.18-0.99, $p=0.046$), when controls without PLE were used as the reference group (Table 7.15).

Table 7.14 Positive schemas in psychosis cases, controls with and controls without PLE

	Cases (n=203)	Controls with PLE (n=35)	Controls without PLE (n=254)
	Median (IQR)	Weighted Median (IQR)	Weighted Median (IQR)
Positive self-schema	13 (7-17)	13 (7-17)	14 (10-17)
Positive other-schema	11 (7-15)	11 (6-16)	13 (10-16)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. IQR, inter-quartile range. PLE, psychotic-like experiences.

Table 7.15 Association between positive schemas and PLE status

	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Positive self-schemas		
Psychosis cases vs. controls without PLE	0.81 (0.54-1.20)	0.85 (0.52-1.38)
Controls with PLE vs. controls without PLE	0.84 (0.37-1.89)	0.66 (0.28-1.54)
Psychosis cases vs. controls with PLE	0.96 (0.42-2.17)	1.29 (0.56-3.00)
Positive other-schemas		
Psychosis cases vs. controls without PLE	0.45 (0.30-0.68)***	0.59 (0.36-0.97)*
Controls with PLE vs. controls without PLE	0.38 (0.16-0.86)*	0.42 (0.18-0.99)*
Psychosis cases vs. controls with PLE	1.20 (0.53-2.73)	1.41 (0.60-3.30)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. OR, odds ratio. CI, confidence interval. PLE, psychotic-like experiences. *p<0.05; **p<0.01; ***p<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class.

When looking at the subsample of participants with cannabis and family history data, controls with PLE continued to show lower positive other-schema scores than controls without PLE, and showed similar median scores to the case subjects (case median: 11 (IQR: 7-15) vs. weighted control with PLE median: 10 (IQR: 5-16) vs. weighted control without PLE median: 12 (IQR: 10-16)), see Table 7.16. Following additional adjustment, any associations found previously between positive other-schemas and case and PLE status were reduced and no longer statistically significant (Table 7.17).

Table 7.16 Positive schemas in psychosis cases, controls with and controls without PLE within the restricted subsample

	Cases (n=85)	Controls with PLE (n=25)	Controls without PLE (n=140)
	Median (IQR)	Weighted Median (IQR)	Weighted Median (IQR)
Positive self-schema	13 (8-16)	14 (6-17)	14 (11-17)
Positive other-schema	11 (7-15)	10 (5-16)	12 (10-16)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. IQR, inter-quartile range. PLE, psychotic-like experiences.

Table 7.17 Association between positive schemas and PLE status, adjusted for other potential confounders in the smaller subsample

	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Positive self-schemas		
Psychosis cases vs. controls without PLE	0.81 (0.45-1.46)	1.04 (0.47-2.27)
Controls with PLE vs. controls without PLE	0.85 (0.31-2.32)	0.61 (0.18-2.04)
Psychosis cases vs. controls with PLE	0.96 (0.35-2.67)	1.69 (0.49-5.86)
Positive other-schemas		
Psychosis cases vs. controls without PLE	0.55 (0.31-0.99)*	1.36 (0.61-3.05)
Controls with PLE vs. controls without PLE	0.50 (0.18-1.39)	0.51 (0.17-1.50)
Psychosis cases vs. controls with PLE	1.09 (0.39-3.04)	2.68 (0.80-8.95)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. OR, odds ratio. CI, confidence interval. PLE, psychotic-like experiences. *p<0.05; **p<0.01; ***p<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class, current cannabis use and family history of psychosis.

7.5. Synergistic effects of social class

In order to address hypothesis 3.1, the next part of this chapter analysed whether severe life events and difficulties combined synergistically with low socio-economic status (SES) to increase the odds of psychotic disorder beyond the effects of each alone. Social class was dichotomised to form a higher social class status category containing the Salariat (classes 1 and 2), and a lower social class status category containing the remaining groups: Intermediate (classes 3, 4, 5, 6); Working Class (classes 7, 8, 9); Never Worked/Long-Term Unemployed (class 10); Students (class 11); and Non-classifiable groups (class 12), (see Methods chapter for further description of the individual class divisions).

Table 7.18 displays the frequencies with which cases and controls were exposed to the individual effects of severe events, difficulties and low SES, and the combined effects of these variables. Four levels were considered: non-exposure, i.e. no/non-severe events/difficulties and high SES, low SES alone, severe events/difficulties alone, and both severe events/difficulties and low SES.

Low SES alone and severe life events alone were both associated with increased odds of psychosis. The weighted adjusted odds ratio for those with low SES only was 3.49 (95% CI 2.07-5.89), and for those exposed to severe life events only it was 3.59 (95% CI 2.04-6.34). The combined effect however, was greater than the sum of these individual effects (OR 14.76 (95% CI 7.46-29.22), interaction contrast ratio (ICR) = 8.68, 95% CI -0.65-18.01, $p=0.068$). The ICR is notably above zero, and is suggestive of additive interaction, although the confidence intervals are wide and so the finding should be treated cautiously. Nonetheless, the ICR tentatively indicates that the odds ratio for psychosis in those with low SES and life events is around 8.68 greater than if there was no synergy between low SES and severe life events.

A similar picture was also seen when considering the impact of low SES on severe difficulties. The individual effects for low SES alone and for severe difficulties alone were both found to increase the odds of psychosis. The weighted adjusted odds ratio for those with low SES only was 4.22 (95% CI 2.44-7.32), and for those exposed to severe difficulties only it was 5.54 (95% CI 3.15-9.74). The combined effect (w.adj. OR 18.80, 95% CI 9.51-37.17, $p<0.001$), however, was again greater than the sum of these individual effects (ICR= 10.04, 95% CI -1.54–21.61, $p=0.089$), which suggests an

additive interaction. Nevertheless, the confidence intervals are wide, and therefore this result can only be interpreted as weak evidence of a synergistic effect.

Table 7.18 Additive interactions between severe life events, difficulties and lower social class status in cases and controls

	Cases (n=253)	Controls (n=301)		
	n (%)	n (w%)	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
No/non-severe events and high SES	53 (21.0)	178 (61.8)	1	1
Low SES	77 (30.4)	59 (16.7)	5.38 (3.32-8.72)***	3.49 (2.07-5.89)***
Severe events	46 (18.2)	48 (17.6)	3.04 (1.78-5.21)***	3.59 (2.04-6.34)***
Events & low SES	77 (30.4)	16 (3.9)	22.82 (11.68-44.61)***	14.76 (7.46-29.22)***
			ICR= 15.40 (95% CI – 0.99-29.81), <i>p</i> = 0.036	ICR= 8.68 (95% CI – 0.65-18.01), <i>p</i> = 0.068
No/non-severe difficulties and high SES	40 (15.8)	168 (58.2)	1	1
Low SES	77 (30.4)	59 (16.2)	6.94 (4.17-11.55)***	4.22 (2.44-7.32)***
Severe difficulties	59 (23.3)	58 (21.2)	4.06 (2.40-6.87)***	5.54 (3.15-9.74)***
Difficulties & Low SES	77 (30.4)	16 (4.5)	25.15 (12.61-50.17)***	18.80 (9.51-37.17)***
			ICR= 15.15 (95% CI - 0.83-31.14), <i>p</i> = 0.063	ICR= 10.04 (95% CI - 1.54-21.61), <i>p</i> = 0.089

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). OR, odds ratio. ICR, interaction contrast ratio. CI, confidence interval. **p*<0.05; ***p*<0.01; ****p*<0.001. ‡, adjusted for age, gender, ethnicity. (Percentages may not add up to 100 due to rounding).

7.6. Synergistic effects of schemas

In order to address hypothesis 3.2, the next part of this chapter analysed whether severe life events and difficulties combined synergistically with a) negative schematic beliefs about the self and b) negative schematic beliefs about others, to increase odds of both psychotic disorder and PLE, beyond the effects of each alone.

7.6.1. Synergistic effects of negative-self schemas on case-control status

Table 7.19 displays the frequencies with which cases and controls reported the individual effects of severe events, difficulties and negative self-schemas and the combined effects of these variables, as well as the unadjusted and adjusted odds ratios for the association with case status. Four levels were considered: non-exposure, i.e. no/non-severe events/difficulties and no negative self-schemas, the individual effects of negative self-schemas, the individual effects of severe events/difficulties, and the combined effect of both severe events/difficulties and negative self-schemas.

The individual effects for negative self-schemas alone and for severe life events alone were both associated with increased odds of psychosis. The weighted adjusted odds ratio for those with negative self-schemas only was 2.28 (95% CI 1.27-4.08), and for those exposed to severe life events only it was 2.36 (95% CI 1.13-4.92). The combined effect of 10.99 (95% CI 5.21-23.15), however, was greater than the sum of these individual effects (interaction contrast ratio (ICR) = 7.35, 95% CI -0.19–14.89, $p=0.056$). The ICR is notably above zero, and is suggestive of additive interaction, although the confidence intervals are wide and so the finding should be treated cautiously. Nonetheless, the ICR tentatively indicates that the odds ratio for psychosis in those with negative self-schemas and severe life events is around 7.35 greater than if there was no synergy between negative self-schemas and severe life events. These results are displayed graphically in Figure 7.1.

A similar picture was also seen when considering the impact of negative self-schemas on severe difficulties. The individual effects for negative self-schemas alone and for severe difficulties alone were both found to increase the odds of psychosis. The weighted adjusted odds ratio for those with negative self-schemas only was 2.72 (95% CI 1.44-5.15), and for those exposed to severe difficulties only it was 4.17 (95% CI 1.99-8.76). The combined effect (w.adj. OR 15.89, 95% CI 7.38-34.24, $p<0.001$), however, was again greater than the sum of these individual effects (ICR= 10.00, 95%

CI -0.65–20.64, $p=0.066$), which suggests existence of additive interaction. Nevertheless, the confidence intervals are wide, and therefore this result can only be interpreted as trend evidence of a synergistic effect. As with events, these results are also displayed graphically in Figure 7.2.

Table 7.19 Additive interactions between severe life events, difficulties and negative self-schemas in cases and controls

	Cases (n=203)	Controls (n=289)		
	n (%)	n (w%)	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
No/non-severe events & no negative schemas	47 (23.2)	147 (48.0)	1	1
Negative self- schemas only	58 (28.6)	84 (31.4)	1.88 (1.15-3.10)**	2.28 (1.27-4.08)**
Severe events only	25 (12.3)	33 (11.9)	2.14 (1.10-4.15)*	2.36 (1.13-4.92)*
Events & schemas	73 (36.0)	25 (8.7)	8.53 (4.75-15.34)***	10.99 (5.21-23.15)***
			ICR= 5.51 (95% CI 0.93-10.09), <i>p</i> = 0.019	ICR= 7.35 (95% CI -0.19- 14.89), <i>p</i> = 0.056
No/non-severe difficulties & no negative schemas	37 (18.2)	141 (45.9)	1	1
Negative self- schemas only	58 (28.6)	78 (28.7)	2.50 (1.48-4.24)***	2.72 (1.44-5.15)**
Severe difficulties only	35 (17.2)	39 (14.0)	3.11 (1.68-5.77)***	4.17 (1.99-8.76)***
Difficulties & schemas	73 (36.0)	31 (11.4)	7.96 (4.43-14.30)***	15.89 (7.38-34.24)***
			ICR= 3.34 (95% CI - 0.78-7.45), <i>p</i> = 0.112	ICR= 10.00 (95% CI -0.65- 20.64), <i>p</i> = 0.066

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). OR, odds ratio. ICR, interaction contrast ratio. CI, confidence interval. **p*<0.05; ***p*<0.01; ****p*<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

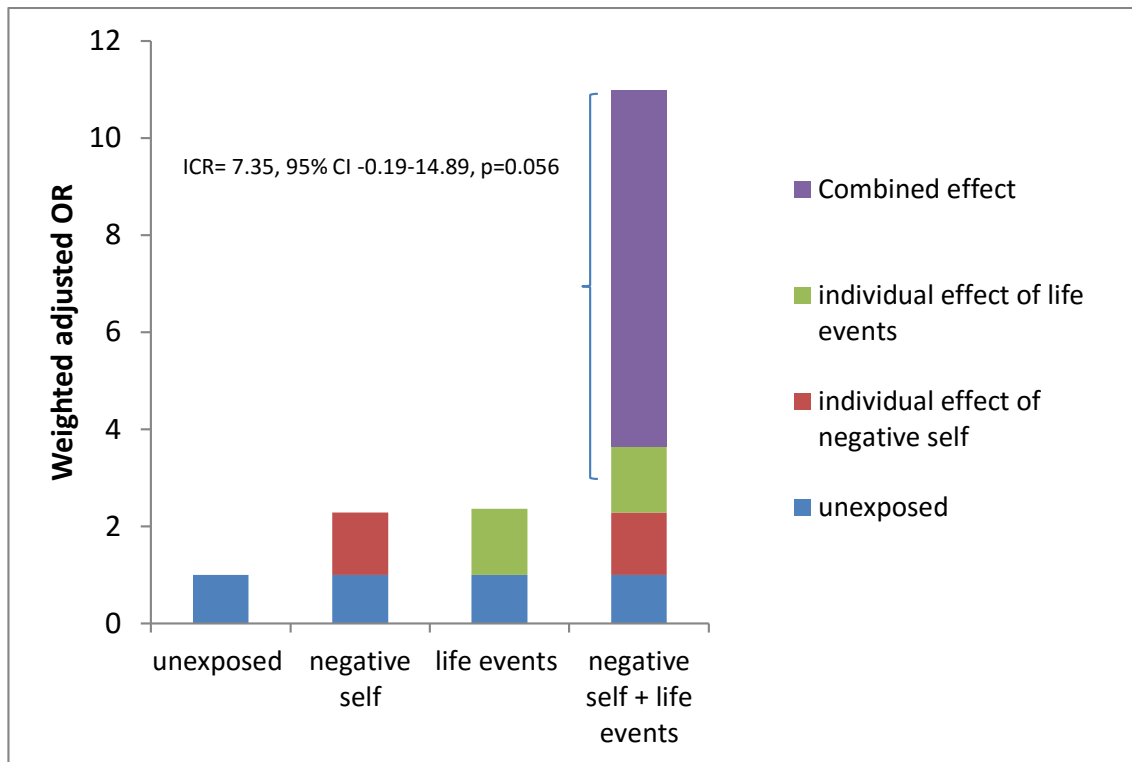


Figure 7.1 Synergistic effects of life events and negative self-schemas in cases and controls

Weighted odds ratio (OR) with 95% confidence intervals (CI), adjusted for age, gender, ethnicity, and main subject social class. Analyses were weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. ICR, interaction contrast ratio.

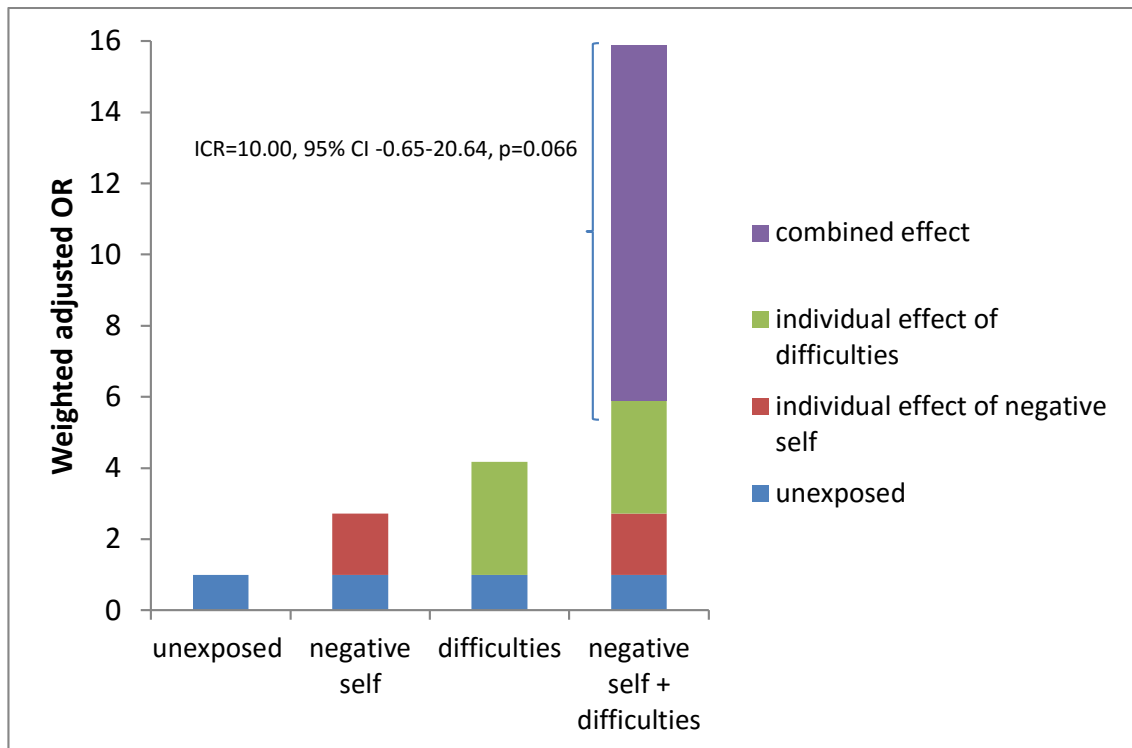


Figure 7.2 Synergistic effects of difficulties and negative self-schemas in cases and controls

Weighted odds ratio (OR) with 95% confidence intervals (CI), adjusted for age, gender, ethnicity, and main subject social class. Analyses were weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. ICR, interaction contrast ratio.

7.6.2. Synergistic effects of negative-self schemas on PLE status

Table 7.20 displays the frequencies with which controls with PLE and controls without PLE reported the individual effects of severe difficulties and negative self-schemas and the combined effects of these variables, to see whether a synergistic effect existed which increased the odds of PLE in controls. These analyses were only performed for difficulties and not for life events as the previous results chapter did not find a statistically significant association between exposure to severe life events and PLE status.

As with any analysis which contains multiple testing, it is likely that there will be an increase in type I error rate, and this is an important caveat to keep in mind when moving on to look at synergistic effects on PLE status, especially due to the small numbers in the PLE group. Any findings need to be interpreted with caution.

There was very weak evidence for a synergistic effect of negative self-schemas in the relationship between severe difficulties and PLE. The ICR was approaching the trend level (ICR= 10.02, 95% CI -4.30–24.35, $p=0.169$), and the individual and combined effects were in the hypothesised directions, i.e. that the odds of PLE were highest in those exposed to difficulties and with negative core beliefs about the self, compared with the odds of having either of these. However, it is evident that for these analyses on PLE status, there was a general lack of power to investigate these associations and to draw any conclusions with confidence.

Table 7.20 Additive interactions between severe difficulties and negative self-schemas in controls with and without PLE

	Controls with PLE (n=35)	Controls without PLE (n=254)		
	n (%)	n (w%)	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
No/non-severe difficulties & no negative schemas	9 (23.9)	132 (48.5)	1	1
Negative self- schemas only	10 (27.3)	68 (28.9)	1.92 (0.67-5.47)	1.59 (0.54-4.72)
Severe difficulties only	5 (11.5)	34 (14.2)	1.64 (0.48-5.61)	2.10 (0.45-9.75)
Difficulties & schemas	11 (37.4)	20 (8.3)	9.09 (2.96-27.94)***	12.72 (3.57-45.35)***
			ICR= 6.54 (95% CI - 2.46-15.54), <i>p</i> = 0.154	ICR= 10.02 (95% CI -4.30- 24.35), <i>p</i> = 0.169

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). OR, odds ratio. ICR, interaction contrast ratio. CI, confidence interval. PLE, psychotic-like experiences. **p*<0.05; ***p*<0.01; ****p*<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

7.6.3. Synergistic effects of negative-other schemas on case-control status

Table 7.21 displays the frequencies with which cases and controls reported the individual effects of severe events and difficulties, and negative other-schemas and the combined effects of the two variables, as well as the unadjusted and adjusted odds ratios for the association with case status. As before, four levels were considered: non-exposure, i.e. no/non-severe events/difficulties and no negative other schema, negative other-schemas, severe events/difficulties, and both severe events/difficulties and negative other-schemas.

In Table 7.21, we can see that the individual effects for negative other-schemas alone and for severe life events alone were both associated with an increased odds of psychosis, and were in the expected direction. The weighted adjusted odds ratio for those with negative other-schemas only was 1.90 (95% CI 1.05-3.45), and for those exposed to severe life events only it was 4.52 (95% CI 2.14-9.57). There was no evidence, however, for an additive interaction between negative other-schemas and severe events (ICR 0.45, 95% CI -3.96-4.87). As was seen previously for events, there is evidence that negative other-schemas alone (w.adj. OR 1.99, 95% CI 1.07-3.72), and severe difficulties alone (w.adj. OR 7.10, 95% CI 3.37-14.97), both independently increased the odds of psychosis. But as before, there was no evidence of an additive interaction between negative other-schemas and severe difficulties (ICR -0.90, 95% CI -6.70-4.90).

Table 7.21 Additive interactions between severe life events, difficulties and negative other-schemas in psychosis cases and controls

	Cases (n=203)	Controls (n=289)		
	n (%)	n (w%)	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
No/non-severe events & no negative schemas	45 (22.2)	137 (49.0)	1	1
Negative other- schemas only	60 (29.6)	94 (30.3)	2.16 (1.32-3.52)**	1.90 (1.05-3.45)*
Severe events only	25 (12.3)	29 (9.8)	2.78 (1.45-5.35)**	4.52 (2.14-9.57)***
Events & schemas	73 (36.0)	29 (10.9)	7.33 (3.97-13.53)***	5.87 (2.98-11.61)***
			ICR= 3.39 (95% CI - 0.74-7.53), p= 0.107	ICR= 0.45 (95% CI -3.96- 4.87), p= 0.840
No/non-severe difficulties & no negative schemas	39 (19.2)	135 (48.3)	1	1
Negative other- schemas only	56 (27.6)	84 (26.3)	2.64 (1.57-4.41)***	1.99 (1.07-3.72)*
Severe difficulties only	31 (15.3)	31 (10.5)	3.66 (1.94-6.91)***	7.10 (3.37-14.97)***
Difficulties & schemas	77 (37.9)	39 (14.8)	6.43 (3.65-11.35)***	7.20 (3.66-14.14)***
			ICR= 1.14 (95% CI - 2.34-4.61), p= 0.521	ICR= -0.90 (95% CI -6.70- 4.90), p= 0.761

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). OR, odds ratio. ICR, interaction contrast ratio. CI, confidence interval. *p<0.05; **p<0.01; ***p<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

7.6.4. Synergistic effects of negative-other schemas on PLE status

Table 7.22 displays the frequencies with which controls with PLE and controls without PLE reported the individual effects of severe difficulties and negative other-schemas and the combined effects of these variables. There was some very weak evidence for a potential synergistic effect of negative other-schemas in the relationship between severe difficulties and PLE, as a much higher proportion of controls with PLE had both severe difficulties and increased negative other-schemas compared with controls without PLE, and the ICR was found to be approaching the trend level (ICR= 10.10, 95% CI -4.42–24.62, $p=0.172$). However, as stated previously, these PLE analyses are greatly lacking in power and only tentative conclusions can be drawn.

Table 7.22 Additive interactions between severe difficulties and negative other-schemas in controls with and without PLE

	Controls with PLE (n=35)	Controls without PLE (n=254)		
	n (%)	n (w%)	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
No/non-severe difficulties & no negative schemas	6 (24.5)	129 (51.1)	1	1
Negative other-schemas only	13 (26.7)	71 (26.3)	2.12 (0.73-6.12)	1.85 (0.62-5.52)
Severe difficulties only	2 (4.9)	29 (11.2)	0.92 (0.15-5.15)	1.25 (0.19-8.39)
Difficulties & schemas	14 (43.9)	25 (11.4)	8.01 (2.52-25.50)***	12.20 (3.26-45.59)***
			ICR= 5.97 (95% CI -1.81-13.75), <i>p</i> = 0.132	ICR= 10.10 (95% CI -4.42-24.62), <i>p</i> = 0.172

w, weighted (for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark). OR, odds ratio. ICR, interaction contrast ratio. CI, confidence interval. PLE, psychotic-like experiences. **p*<0.05; ***p*<0.01; ****p*<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

7.7. Affective Symptoms

7.7.1. Affective symptoms and case-control status

In order to address hypothesis 4.1, this next section assessed whether cases reported greater levels of anxiety and depression compared with controls. Examination of Table 7.23 reveals that as hypothesised, cases showed higher levels of anxiety compared with controls (case median: 7 (IQR: 3-13) vs. weighted control median: 3 (IQR: 2-6)). An increase in anxiety scores (cut at the median) was associated with an increase in the odds of psychosis (w.adj. OR 3.20, 95% CI 1.96-5.21, $p < 0.001$) (Table 7.24). Similarly and as hypothesised, cases also showed higher levels of depression compared with controls (case median 6 (IQR: 3-11) vs. weighted control median: 3 (IQR: 1-5)), see Table 7.23. An increase in depression scores (cut at the median) was also associated with an increase in the odds of psychosis (w.adj. OR 2.77, 95% CI 1.68-4.58, $p < 0.001$) (Table 7.24).

Table 7.23 Median affective symptom scores in psychosis cases and controls at the time of assessment

	Cases (Anxiety: n=206) (Depression: n=187)	Controls (n=287)
	Median (IQR)	Weighted Median (IQR)
Anxiety scores	7 (3-13)	3 (2-6)
Depression scores	6 (3-11)	3 (1-5)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. IQR, inter-quartile range.

Table 7.24 Association between affective symptoms and psychotic disorder

	Cases	Controls					
	n (%)	n (w%)	χ^2 †	df †	p†	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Anxiety	(n=206)	(n=287)					
Low (0-4)	66 (32.0)	172 (58.7)	34.34	1	<0.001	1	1
High (5-56)	140 (68.0)	115 (41.3)				3.01 (2.02-4.51)***	3.20 (1.96-5.21)***
Depression	(n=187)	(n=287)					
Low (0-3)	59 (31.6)	167 (57.7)	31.35	1	<0.001	1	1
High (4-54)	128 (68.5)	120 (42.3)				2.96 (1.96-4.48)***	2.77 (1.68-4.58)***

w, weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. † calculated using weights. df, degrees of freedom. OR, odds ratio. CI, confidence interval. *p<0.05; **p<0.01; ***p<0.001. ‡ adjusted for age, gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

When looking at the subsample of participants with cannabis and family history data, the median values and IQR altered slightly but cases continued to have higher levels of anxiety compared with controls (case median: 6 (IQR: 3-10) vs. weighted control median: 3 (IQR: 1-5)), see Table 7.25. An increase in anxiety scores was still associated with an increase in the odds of psychosis (w.adj. OR 2.53, 95% CI 1.13-5.66, $p=0.024$), following this additional adjustment (Table 7.26).

As before in the full sample, cases were found to have higher levels of depression compared with controls (case median 5 (IQR: 2-9) vs. weighted control median: 3 (IQR: 1-5)), see Table 7.25. An increase in depression scores was associated with an increase in the odds of psychosis (w.adj. OR 2.01, 95% CI 0.90-4.49, $p=0.089$) (Table 7.26). However, this association no longer met standard levels of statistical significance after additional adjustment, and is potentially limited by the substantial decrease in sample size.

Table 7.25 Median affective symptom scores in psychosis cases and controls at the time of assessment, adjusted for other potential confounders in the smaller subsample

	Cases (Anxiety: n=83) (Depression: n=80)	Controls (n=165)
	Median (IQR)	Weighted Median (IQR)
Anxiety scores	6 (3-10)	4 (2-7)
Depression scores	5 (2-9)	3 (1-5)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. IQR, inter-quartile range.

Table 7.26 Association between affective symptoms and psychosis, adjusted for other potential confounders in the smaller subsample

	Cases	Controls					
	n (%)	n (w%)	χ^2 †	df †	p†	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Anxiety	(n=83)	(n=165)					
Low (0-4)	27 (32.5)	103 (58.7)	15.12	1	<0.001	1	1
High (5-56)	56 (67.5)	62 (41.3)				2.95 (1.62-5.34)***	2.53 (1.13-5.66)*
Depression	(n=80)	(n=165)					
Low (0-3)	28 (35.0)	94 (56.2)	9.67	1	0.004	1	1
High (4-54)	52 (65.0)	71 (43.8)				2.38 (1.32-4.30)**	2.01 (0.90-4.49)

w, weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. † calculated using weights. df, degrees of freedom. OR, odds ratio. CI, confidence interval. *p<0.05; **p<0.01; ***p<0.001. ‡ adjusted for age, gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

7.7.2. Affective symptoms and PLE status

In order to address hypothesis 4.2, this next section assessed whether controls with PLE reported greater levels of anxiety and depression compared with controls without PLE. Tables 7.27-7.30 show the associations between affective symptoms and psychosis in cases, and controls with and without PLE. Interestingly, controls with PLE had higher levels of anxiety than controls without PLE, and they showed similar median scores to the case subjects (case median 7 (IQR: 3-13) vs. weighted control with PLE median: 7 (IQR: 3-12) vs. weighted control without PLE median: 3 (IQR: 1-6)), see Table 7.27. An increase in anxiety scores was associated with both an increase in the odds of PLE (w.adj. OR 3.16, 95% CI 1.33-7.50, $p=0.009$) and psychotic disorder (w.adj. OR 3.78, 95% CI 2.26-6.34, $p<0.001$) (Table 7.28).

Table 7.27 Affective symptom scores at the time of assessment in psychosis cases, controls with and controls without PLE

	Cases (Anxiety: n=206) (Depression: n=187)	Controls with PLE (n=35)	Controls without PLE (n=252)
	Median (IQR)	Weighted Median (IQR)	Weighted Median (IQR)
Anxiety scores	7 (3-13)	7 (3-12)	3 (1-6)
Depression scores	6 (3-11)	7 (2-10)	3 (1-5)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. IQR, inter-quartile range. PLE, psychotic-like experiences

When looking at the depression scores across cases, and controls with and without PLE, a similar pattern to anxiety is also seen. Controls with PLE had higher levels of depression than controls without PLE, and they also showed similar median scores to the case subjects (case median 6 (IQR: 3-11) vs. weighted control with PLE median: 7 (IQR: 2-10) vs. weighted control without PLE median: 3 (IQR: 1-5)), see Table 7.27. Furthermore, an increase in levels of current depression was associated with both an increase in the odds of PLE (w.adj. OR 3.19, 95% CI 1.29-7.88, $p=0.012$) and psychotic disorder (w.adj. OR 3.26, 95% CI 1.92-5.53, $p<0.001$) (Table 7.28).

Table 7.28 Association between anxiety, depression and PLE status

	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Anxiety		
Psychosis cases vs. controls without PLE	3.43 (2.25-5.21)***	3.78 (2.26-6.34)***
Controls with PLE vs. controls without PLE	3.33 (1.46-7.57)**	3.15 (1.33-7.50)**
Psychosis cases vs. controls with PLE	1.03 (0.45-2.34)	1.20 (0.50-2.85)
Depression		
Psychosis cases vs. controls without PLE	3.40 (2.22-5.22)***	3.26 (1.92-5.53)***
Controls with PLE vs. controls without PLE	3.71 (1.58-8.75)**	3.19 (1.29-7.88)**
Psychosis cases vs. controls with PLE	0.92 (0.39-2.17)	1.02 (0.41-2.54)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. OR, odds ratio. CI, confidence interval. PLE, psychotic-like experiences. *p<0.05; **p<0.01; ***p<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class.

Following adjustment for the additional confounders of current cannabis use and family history of psychosis (see Tables 7.29 and 7.30), controls with PLE continued to show higher levels of anxiety compared with controls without PLE (case median 6 (IQR: 3-10) vs. weighted control with PLE median: 7 (IQR: 4-12) vs. weighted control without PLE median: 3 (IQR: 1-5)), see Table 7.29. As before, an increase in anxiety was associated with both an increase in the odds of PLE (w.adj. OR 4.64, 95% CI 1.60-13.52, p=0.005) and psychotic disorder (w.adj. OR 3.46, 95% CI 1.46-8.18, p=0.005) (Table 7.30).

After adjustment for these additional factors, cases and controls with PLE continued to have high levels of depression compared with controls without PLE (case median 5 (IQR: 2-9) vs. weighted control with PLE median: 8 (IQR: 4-10) vs. weighted control without PLE median: 3 (IQR: 1-5)), see Table 7.29. As with the full sample, an increase in levels of current depression remained associated with both an increase in the

odds of PLE (w.adj. OR 4.86, 95% CI 1.53-15.45, p=0.008) and psychotic disorder (w.adj. OR 2.80, 95% CI 1.20-6.56, p=0.018) (Table 7.30).

Table 7.29 Affective symptom scores at the time of assessment in psychosis cases, controls with and controls without PLE within the restricted subsample

	Cases (Anxiety: n=83) (Depression: n=80)	Controls with PLE (n=25)	Controls without PLE (n=140)
	Median (IQR)	Weighted Median (IQR)	Weighted Median (IQR)
Anxiety scores	6 (3-10)	7 (4-12)	3 (1-5)
Depression scores	5 (2-9)	8 (4-10)	3 (1-5)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. IQR, inter-quartile range. PLE, psychotic-like experiences.

Table 7.30 Association between anxiety, depression and PLE status, adjusted for other potential confounders in the smaller subsample

	Weighted unadjusted OR (95% CI)	Weighted adjusted OR‡ (95% CI)
Anxiety		
Psychosis cases vs. controls without PLE	3.63 (1.93-6.84)***	3.46 (1.46-8.18)**
Controls with PLE vs. controls without PLE	4.98 (1.76-14.03)**	4.64 (1.60-13.52)**
Psychosis cases vs. controls with PLE	0.73 (0.25-2.09)	0.74 (0.22-2.47)
Depression		
Psychosis cases vs. controls without PLE	2.91 (1.56-5.41)***	2.80 (1.20-6.56)*
Controls with PLE vs. controls without PLE	4.88 (1.64-14.51)**	4.86 (1.53-15.45)**
Psychosis cases vs. controls with PLE	0.60 (0.20-1.81)	0.58 (0.17-1.95)

Weighted for the population proportions of age, gender and ethnicity according to Census values within Lambeth & Southwark. OR, odds ratio. CI, confidence interval. PLE, psychotic-like experiences. *p<0.05; **p<0.01; ***p<0.001. ‡, adjusted for age, gender, ethnicity, main subject social class, current cannabis use and family history of psychosis.

7.8. Mediation via affective symptoms

In order to investigate the final hypothesis 4.3, this next section analysed the association between recent life events, difficulties and psychosis (both clinical disorder and psychotic experiences in the control sample) to see whether these relationships were mediated by a) higher levels of depression and b) higher levels of anxiety.

To investigate pathways from severe life events and difficulties to psychosis via affective symptoms, estimates of the total effects of life events and difficulties on psychotic disorder and PLE were parsed into direct effects and indirect effects using multiple mediation analyses. The direct effect is the effect of severe life events and difficulties on psychosis when controlling for depression and anxiety. The indirect effect is the mediating effect and shows the effect of severe life events and difficulties on psychosis via the pathways of depression and anxiety.

7.8.1. Mediation by anxiety and depression

Severe events

The total, direct and indirect effects of severe events and affective symptoms on case-control status are presented in Table 7.31. The combination of anxiety and depression mediated 15.2% of the total effect which suggests some evidence of partial mediation. However, neither of the two indirect effects were statistically significant as the confidence intervals both contained zero (direct effect: adj. standardised coefficient 0.294, 95% CI 0.170-0.386; indirect effect of anxiety: adj. standardised coefficient 0.036, 95% CI -0.002-0.080, percentage mediated= 10.3%; indirect effect of depression: adj. standardised coefficient 0.017, 95% CI -0.004-0.056, percentage mediated= 4.9%).

Table 7.31 Total, direct and total indirect effects of severe life events and affective symptoms on case-control status

	Unadjusted standardized coefficient (95% CI)	% of total effect	Adjusted standardized coefficient‡ (95% CI)	% of total effect
Direct effect	0.269 (0.181-0.358)	83.8	0.294 (0.170-0.386)	84.5
Indirect effect- anxiety	0.028 (0.002-0.067)	8.7	0.036 (-0.002-0.080)	10.3
Indirect effect- depression	0.025 (0.003-0.058)	7.8	0.017 (-0.004-0.056)	4.9
Total effect	0.321 (0.235-0.418)	-	0.348 (0.190-0.446)	-

CI, confidence interval. ‡, adjusted for age, gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

Severe difficulties

Table 7.32 displays the total, direct and indirect effects of severe difficulties, anxiety and depression on case-control status. As was found for severe events, there was some evidence suggestive of partial mediation by affective symptoms as the combination of anxiety and depression mediated 17.1% of the total effect. The mediating effect was mainly driven by the significant effect of anxiety as the indirect effect of depression was not statistically significant (confidence interval contained zero) (direct effect: adj. standardised coefficient 0.319, 95% CI 0.211-0.433; indirect effect of anxiety: adj. standardised coefficient 0.047, 95% CI 0.004-0.098, percentage mediated= 12.2%; indirect effect of depression: adj. standardised coefficient 0.019, 95% CI -0.024-0.069, percentage mediated= 4.9%).

Table 7.32 Total, direct and total indirect effects of severe difficulties and affective symptoms on case-control status

	Unadjusted standardized coefficient (95% CI)	% of total effect	Adjusted standardized coefficient‡ (95% CI)	% of total effect
Direct effect	0.232 (0.129-0.339)	77.3	0.319 (0.211-0.433)	82.9
Indirect effect- anxiety	0.037 (0.007-0.084)	12.3	0.047 (0.004-0.098)	12.2
Indirect effect- depression	0.031 (-0.006-0.742)	10.3	0.019 (-0.024-0.069)	4.9
Total effect	0.300 (0.202-0.404)	-	0.385 (0.271-0.487)	-

CI, confidence interval. ‡, adjusted for age, gender, ethnicity, main subject social class. (Percentages may not add up to 100 due to rounding).

7.8.2. Mediation by anxiety and depression on PLE status

The total, direct and indirect effects of severe difficulties, anxiety and depression were also considered for controls with PLE and controls without PLE to see whether these affective processes may mediate the relationship between severe difficulties and PLE. These analyses were only performed for difficulties and not for life events as the previous results chapter did not find a statistically significant association between exposure to severe life events and PLE status.

Due to small numbers, it was not possible to retrieve bootstrap standard errors and 95% confidence intervals for the adjusted analysis and so only the unadjusted results are presented below as tentative and exploratory.

Severe difficulties

The total, direct and indirect effects of severe difficulties and affective symptoms on PLE status are presented in Table 7.33. The combination of anxiety and

depression mediated 24.2% of the total effect which suggests some evidence of partial mediation. The unadjusted coefficients suggest the mediating effect is likely to be driven by depression as the indirect effect for anxiety was not significant (direct effect: unadj. standardised coefficient 0.199, 95% CI 0.014-0.347; indirect effect of anxiety: unadj. standardised coefficient 0.007, 95% CI -0.035-0.056, percentage mediated= 2.7%; indirect effect of depression: unadj. standardised coefficient 0.056, 95% CI 0.010-0.136, percentage mediated= 21.5%).

Table 7.33 Total, direct and total indirect effects of severe difficulties and affective symptoms in controls with and without PLE

	Unadjusted standardized coefficient (95% CI)	% of total effect
Direct effect	0.199 (0.014-0.347)	76.2
Indirect effect- anxiety	0.007 (-0.035-0.056)	2.7
Indirect effect- depression	0.056 (0.010-0.136)	21.5
Total effect	0.261 (0.083-0.420)	-

CI, confidence interval. PLE, psychotic-like experiences. (Percentages may not add up to 100 due to rounding).

7.9. Overview of findings

The original study hypotheses tested in this chapter are restated in Table 7.34, along with a concise summary of the relevant results and an indication of whether each hypothesis was supported or not. Of the six hypotheses assessed in this chapter, four were fully supported by the evidence obtained, and two hypotheses were partially supported.

7.10. Summary of Chapter 7

The aim of this chapter was to explore the synergistic effects of low social class, and negative core schemas, and the mediating effects of affective symptoms in the relationship between severe life events and difficulties and the onset of psychotic disorder and PLE.

Firstly, and as hypothesised, it was found that psychosis cases had an increase in negative self-schemas and negative other-schemas compared with control subjects. Controls with PLE were also found to have similar levels of negative self-schemas and negative other-schemas as cases. There was no difference found between cases and controls for positive self-schemas but cases did show reduced positive other-schemas compared with controls. When considering PLE status, controls with PLE did not significantly differ from controls without PLE or from cases for their levels of positive self-schemas. However, controls with PLE did show similar levels of positive other-schemas as cases and this was significantly lower than controls without PLE.

There was weak (but suggestive) evidence of synergistic effects for severe life events and difficulties and social class; although the confidence intervals were very wide. As hypothesised, the odds of psychotic disorder were highest in those exposed to severe life events and difficulties and with low SES.

In relation to the synergistic effects of negative core schemas, as hypothesised, the odds of psychotic disorder was highest in those exposed to severe life events and difficulties and with negative beliefs about the self, but against what was hypothesised, there was no similar effect found for negative other-schemas. There was also some evidence for a synergistic effect of severe difficulties and negative self-schemas on odds of PLE. Unlike for psychotic disorder, there was a possible trend found for negative

other-schemas in that the effect of severe difficulties depended on negative other-schemas to increase the odds of PLE.

In terms of affective processes, as hypothesised, cases had increased levels of anxiety and depression compared with controls and the controls with PLE showed similar levels to cases. Less consistent evidence was found for affective symptoms as a mediator of the relationship between severe life events/difficulties and psychotic disorder or PLE.

Table 7.34 Summary of Chapter 7 findings in relation to the original study hypotheses

Hypothesis	Supported?	Specific results
<i>2.1. Cases will report higher levels of negative schematic beliefs about the self and about others compared with controls</i>	Yes	<ul style="list-style-type: none">- Increased levels of negative self-schemas were associated with increased odds of psychosis***- Increased levels of negative other-schemas were associated with increased odds of psychosis**
<i>2.2. Controls with PLE will report higher levels of negative schematic beliefs about the self and about others compared with controls without PLE</i>	Yes	<ul style="list-style-type: none">- Increased levels of negative self-schemas were associated with increased odds of PLE**- Increased levels of negative other-schemas were associated with increased odds of PLE**
<i>3.1. Severe life events and difficulties will combine synergistically with lower social class status to increase the odds of psychotic disorder beyond the effects of each alone</i>	Yes	<ul style="list-style-type: none">- Weak (but suggestive) evidence of synergistic effects for severe life events, difficulties, and low SES; although confidence intervals were very wide
<i>3.2. Life events and difficulties will combine synergistically with a) negative schematic beliefs about the self and b) negative schematic beliefs about others, to increase odds of both psychotic disorder and PLE, beyond the effects of each alone.</i>	Partial	<ul style="list-style-type: none">- Weak evidence of a synergistic effect of severe life events and negative self-schemas on odds of psychotic disorder (p=0.056) and a similar effect found for negative self-schemas, severe difficulties and psychotic disorder (p=0.066)- Very weak evidence of synergistic effects of severe difficulties and negative self-schemas on odds of PLE (p=0.169)- No evidence of synergistic effects of severe events/difficulties and negative other-schemas on odds of psychotic disorder- Very weak evidence of synergistic effects of severe difficulties and negative other-schemas on odds of PLE (p=0.172)
<i>4.1. Cases will report greater levels of anxiety and depression</i>	Yes	<ul style="list-style-type: none">- Increased levels of anxiety*** and depression*** were associated with

Hypothesis	Supported?	Specific results
<i>compared with controls</i>		increased odds of psychosis
<i>4.2. Controls with PLE will report greater levels of anxiety and depression compared with controls without PLE</i>	Yes	- Increased levels of anxiety** and depression** were associated with increased odds of PLE
<i>4.3. The association between recent life events, difficulties and psychosis (both clinical disorder and psychotic experiences in the control sample) will be mediated by a) higher levels of depression and b) higher levels of anxiety</i>	Partial	<ul style="list-style-type: none"> - There were no significant mediating effects of severe life events and psychotic disorder via anxiety and depression - Depression was not a significant mediator of the association between severe difficulties and psychotic disorder but anxiety accounted for 12.2% of the total effect - Anxiety was not a significant mediator of the association between severe difficulties and PLE but depression accounted for 21.5% of the unadjusted total effect

*p<0.05; **p<0.01; ***p<0.001.

CHAPTER 8 – Discussion

Synopsis

The aim of this final chapter is to provide a synthesised overview of the thesis. After providing an overall summary of the key findings, it will present a discussion of the key methodological issues in this study. Subsequently, there will be an attempt to tie the key findings together in relation to previous research findings. This chapter will end with a short discussion highlighting some of the possible clinical implications of this research and implications for future research on life events and psychosis.

8.1. Summary of findings

Chapter 5 described the basic demographics of cases and controls within the full CAPsy study sample at interview, at onset (cases only), and one year pre-onset/interview. Cases differed from controls in the expected ways, e.g. cases were younger (e.g. DeLisi, 1992), more often men (e.g. Aleman et al., 2003), more often from minority ethnic groups (e.g. Fearon et al., 2006), and more often disadvantaged and isolated on a number of markers (e.g. Morgan et al., 2008). These findings were also found to hold at all time-points presented, with the effects becoming stronger closer to interview, suggesting some degree of downward social drift in the period pre- and post-onset; ideas which have been proposed and supported in previous research studies (e.g. Dohrenwend et al., 1992; Stilo et al., 2013).

Again, similarly to previous research findings, controls with PLE were found to differ from controls without PLE with regard to ethnicity, i.e. more likely to come from minority ethnic backgrounds, and education level, i.e. less likely to have attained a higher education level (e.g. Johns et al., 2004); Morgan et al., 2009). Furthermore, for some variables, controls with PLE showed intermediate values between cases and controls without PLE, and these included parental and subject social class, current relationship status, living arrangement, family history of psychosis, and current cannabis use.

Chapter 6 explored the associations between the different characteristics of life events and difficulties one year pre-onset/interview and psychosis. Taking each hypothesis in turn:

- 1) There was no evidence that an increased prevalence of life events and difficulties was associated with increased odds of psychosis when experiences at any level of severity were considered.
- 2) There was evidence that exposure to severe and intrusive experiences over the one year prior to onset was particularly associated with psychosis, showing a three- to twelve-fold increase in odds, and the impact of severe events and difficulties was found to be cumulative.
- 3) There was partial evidence that exposure to severe experiences was associated with increased odds of PLE, with effects found for severe difficulties but not for severe life events.
- 4) There was partial evidence that gender moderated the relationship between severe life events and psychosis, such that the effect was stronger in men than women, but no gender effects were found for severe difficulties. More robust evidence was found for age, whereby the odds of psychosis following severe life events and difficulties were higher for those aged less than 30 years than those aged above 30 years. No age or gender effects were found for intrusive events and difficulties.
- 5) There was some evidence that exposure to independent experiences was also associated with increased odds of psychosis, with an effect found for independent life events but not for difficulties.
- 6) There was evidence that the odds of psychosis were higher in those who had experienced solely subject-focused events and difficulties.
- 7) There was some evidence that the odds of psychosis were higher for those who had experienced events closer to onset, with cases found to be exposed to more severe events in the final three weeks prior to onset but these findings were limited by small numbers.

Chapter 7 explored synergistic effects of low social class and negative schemas and mediation by affective symptoms in the associations between exposure to severe life events and difficulties and presence of psychosis. Taking each hypothesis in turn:

- 1) There was evidence that cases had higher levels of negative self-schemas and negative other-schemas compared with controls.

- 2) There was also evidence that controls with PLE had higher levels of negative self- and other-schemas compared with controls without PLE, and showed similar levels to cases.
- 3) There was weak, but suggestive evidence of synergistic effects for severe life events, difficulties, and low SES.
- 4) There was some evidence of synergistic effects of negative schemas and life events/difficulties, with the odds of psychotic disorder being highest in those exposed to severe life events and difficulties and with negative self-schemas. However, synergistic effects were not found for life events and difficulties and negative other-schemas, and very weak evidence was found of synergistic effects of severe difficulties and both negative self and other schemas on odds of PLE.
- 5) There was evidence that cases had increased levels of anxiety and depression compared with controls.
- 6) There was also evidence that the controls with PLE had increased levels of affective symptoms compared with controls without PLE, and showed similar levels to cases.
- 7) Less consistent evidence was found for affective symptoms as a mediator of the relationship between severe life events/difficulties and psychotic disorder or PLE.

8.2. Methodological issues

Although many of the findings presented in this thesis are consistent with previous research, this study is not without limitations, many of which are related to the general pitfalls of a case-control study design.

There are two main analytic epidemiological study designs: cohort and case-control. Cohort studies begin by selecting individuals exposed to and not exposed to candidate causal factors, and follow them over time to determine who develops the outcome (or disorder) of interest. A case-control study involves identifying cases with a disorder of interest and comparing them with unaffected controls. The researchers use retrospective assessments to determine the exposure status of both cases and controls to see whether specific exposures are associated with an increase in odds of the outcome under study.

A cohort design could be used to answer the research questions of this thesis by identifying groups exposed and not exposed to recent life events, and then following them over time (e.g. one year) to see to determine the relative risk of disorder. However,

the key limitation to this approach is that psychosis is a rare disorder with an incidence of around 20 per 100,000 per year (McGrath, 2007); and so many thousands of individuals would need to be followed up in order to find each case of psychosis. Therefore, these low incidence figures give an idea of the scale needed when using a cohort design to look at risk factors for psychotic disorders.

The alternative to a cohort study, and what has been employed in this thesis, is to use a case-control design. This is a more efficient design for studying a rare disorder such as psychosis, and for studying multiple exposures. However, this type of study design, has three central challenges: firstly, selecting cases and controls from the same source population (i.e., selection bias), secondly, establishing the temporal order of exposure and disease (i.e., reverse causality), and thirdly, obtaining an unbiased measure of the exposure with retrospective measurement (i.e., information bias). It is critical to ensure these challenges have been met before concluding that an observed association between an exposure and outcome is valid. There are four key principles, the so called “mantra” of epidemiology, which should be considered in order to determine whether an observed association is a true association. These principles are bias, confounding, chance, and reverse causality, and a discussion of how each of these are applicable to the study in question will be discussed below.

8.2.1. Bias

Bias is systematic error either arising from the design or execution of a study. Unlike confounding, bias cannot be controlled for in the analysis stage of a project and requires careful planning during the design stage in order to minimise its effects on the final results. However, no study will ever be truly free from bias and so some care must always be taken when drawing inferences about cause and effect. There are two main forms of non-random bias. The first originates when selecting the sample population under study, and this is known as ‘selection bias’. The second can arise during the measurement stage and this is known as ‘information bias’.

Selection Bias

Selection bias is a major methodological issue for case-control studies, and ensuring its absence is seen as one of the most important conditions to be met (Susser et al., 2006). To minimise this type of bias, “cases selected for the study should be

representative of all cases from the base population and all controls should be representative of all controls” (Stewart, 2003: 229). Selection bias can occur where the selection of a case or control is somehow related to the exposure or outcome under study. For example, selection bias could have occurred in this particular study if selection into the study was related to the occurrence of life events and difficulties. This is more serious if the bias overestimates exposure to life events in cases (or underestimates exposure to life events in controls), as this can inflate the size of the association found between life events and psychosis.

Firstly, bias may have occurred in the selection of cases if those who took part were more likely to report exposure to recent life events and difficulties. Bias may have arisen if the study systematically sampled less well cases (because those who were better were discharged early, etc.). This could potentially bias estimates of the association between life events and psychosis because those who are less well and stay in hospital for longer, may be more likely to experience recent life events and difficulties. As a result, this would over-estimate the prevalence of life events in cases, and the difference between cases and controls is therefore artificially inflated.

Conversely, if the study systematically selected well-adjusted controls, bias may have occurred if those who did not report exposure to life events were more likely to take part. It is plausible to see how this may have occurred as those who respond and are willing to take part in research studies may be more together, better off, etc. and so experience fewer life events. As a result, the prevalence of life events in the population (controls) is underestimated, and the difference between cases and controls in terms of the association between life events and psychosis, is artificially inflated.

It is also possible that the biases go in the other direction, i.e. those cases recruited were less likely to report life events (or controls were more likely to report life events). Biases that underestimate life events in cases or that overestimate life events in controls can result in an artificially reduced association. Given that considerably large effects between life events and psychosis were found in this thesis, this is not as serious an issue, and the first set of biases (over-estimate of the effect) is likely to be more problematic.

With the possibility of these biases in mind, careful consideration was given to try to minimise the effects of selection bias during the design of the study. Firstly, the sample was recruited to be as representative as possible. For cases, this meant

attempting to recruit a sample which was representative of all cases of first episode psychosis who resided in the catchment areas during the course of study recruitment. Bias can occur through using a convenience sampling method to recruit cases and by selecting participants from only one source, e.g. from inpatient units only. These methods can, for example, lead to a sample which is overrepresented by individuals with the most severe form of the disease, and therefore with the potential to report exposure to more life events and difficulties. In this study, a considerable effort was made to recruit cases from a variety of sources, e.g. from various inpatient and community services, as well as home treatment teams, specialist early intervention services and forensic services. This was done to ensure that the sample was not biased by recruiting individuals with a more severe presentation. However, there will inevitably be individuals who were missed. For example, some people who experience an onset of psychosis do not present to specialist mental health services; either they will decide not to seek help, or they will only be seen by primary care services. Furthermore, there will also be individuals who did present to secondary mental health services, but were not recruited into this study. These ‘missed’ individuals can be seen in the case recruitment flow chart (Figure 4.1, Chapter 4), where reasons for non-approach included individuals being discharged from services, not attending appointments where the study could be introduced, or they had moved out of area.

It is clear that these reasons could introduce different selection biases into the study, e.g. if we systematically recruited individuals who were not granted an earlier discharge, the recruited sample may be more likely to include more severe and chronic cases who have experienced more stressful events, and this may overinflate associations between stressful exposures and psychosis. Furthermore, if the study was not able to recruit individuals who missed appointments, or had more chaotic lives full of frequent life events, this could mean that these more unstable individuals were not included in the research sample. As a result, this would then underestimate an association between stress and psychosis onset. Unfortunately, due to the large number of potential cases that were being screened on a weekly basis, it was not feasible to record the exact number of missed cases for the reasons listed above, and use this information to see how it may have influenced the findings. This is clearly an important consideration for future studies.

Rigorous steps were also taken to reduce selection bias when recruiting the control participants. Two methods of random sampling were used to recruit controls-

either via GP surgeries and GP lists, or via the ongoing SELCoH study which used the Postcode Address File (PAF). The combination of these two independent methods was intended to minimise the biases associated with using each on its own. For example if a person works full-time and is rarely at home, it may be difficult to recruit them via PAF sampling; however, they may be more likely to be recruited after receiving a letter of invitation from their GP. Encouragingly, the overall control sample was found to be broadly representative of the population living within the catchment boroughs, and data were weighted to account for any imbalances due to over-sampling of certain groups. However, selection bias cannot be completely eliminated by using this dual approach to control recruitment.

Even though the overall control sample was found to be representative of the local population, there may well be differences that exist between the two sampling methods. Although this thesis did not analyse possible differences between the two control recruitment methods, there are a variety of potential differences that could be hypothesised. One possibility is that individuals recruited via the PAF may be more likely to contain older, retired individuals who are less likely to experience life events (Bebbington et al., 1991; Norris, 1992). As a result, if the PAF method is more likely to systematically select older, more well-adjusted controls, then this could potentially lead to bias in the estimates of life events and psychosis, as those who are well-adjusted have fewer life events. This would therefore underestimate the prevalence of life events in this control group and the difference between cases and controls would be artificially inflated. However, this study did employ quota sampling to ensure that the control sample was broadly representative of the local population in terms of age, gender and ethnicity. Therefore, there was a strong attempt to reduce the oversampling of certain groups.

Control selection via GP lists may have also introduced possible bias into the study findings. The sample recruited via GP lists may contain a greater number of migrants compared with the PAF approach. A major attraction of migrating to the UK is the availability of free NHS healthcare, and anyone intending to be in the UK for longer than three months is allowed to register for a GP. In terms of how this may have influenced the findings of this thesis, if there is a greater proportion of migrants who have fled countries in conflict, then this is likely to have an impact on the nature and severity of recent experiences that would be reported by these individuals. This could lead to increased reporting of certain traumatic events within this control group, than

what may be found in the PAF sample. Therefore, a potential overestimation of certain severe life events by controls in the GP sampled group could result in an artificially reduced association between life events and psychosis. However, as mentioned above, the use of quota sampling was intended to minimise this possibility affecting the findings as it restricted the oversampling of certain minority groups.

In summary, different sampling methods have the potential to produce systematic differences in the type of individuals they identify. Nevertheless, the use of both sampling methods is likely to have enabled access to some individuals who may have otherwise been missed, and therefore the present control sample may be more representative as a result.

Methods used to ‘balance the odds’ were likely to have increased the representativeness of controls. Cases and controls were both drawn from the same source population, i.e. from the London boroughs of Lambeth and Southwark. Furthermore, controls were not excluded if they had a psychiatric diagnosis other than psychosis, which ensured that the differences between cases and controls were not overinflated due to having a sample consisting of only ‘well controls’ (Schwartz & Susser, 2011). Furthermore, controls were screened for a history of psychosis using the PSQ (Bebbington & Nayani, 1995), and if they were deemed to have a psychotic disorder, they were transferred to the case arm of the study. This scenario did occur for one control participant.

However, differences in the findings may have arisen due to not recruiting a ‘mentally healthy’ control sample. As life events have been shown to be associated with a variety of mental disorders other than psychosis (Harris, 2000), the fact that life events did not increase the odds of psychosis in this control sample does not mean that controls who were exposed to recent stressful experiences did not experience changes to their mental health. Some controls may well have experienced an onset or exacerbation of depression or anxiety that could be partially attributed to recent stress. If we were to exclude these individuals with other disorders (and therefore more stresses), then associations between life events and psychotic disorder could become more exaggerated, i.e. the effect becomes stronger. However, excluding all controls with a non-psychotic disorder would then make the sample unrepresentative of the general population.

Interestingly, the controls were found to be representative in terms of the prevalence of severe life events experienced within the previous year, when compared to a larger sample of the same source population. Evidence of this is given by comparable rates of recent life events within the wider SELCoH study. This study interviewed almost 1700 adults from 1075 randomly selected households across the London boroughs of Lambeth and Southwark. The prevalence of severe life events experienced over the past year in this thesis was 21.5% (n=64), which is comparable to the rates found in a larger sample from the same local population (25%, n=422), (Morgan et al., 2014). However, although this is reassuring, it is also important to bear in mind that the measures used to assess life events in these two studies were very different, i.e. semi-structured interview used in this thesis vs. a checklist approach used in the Morgan et al. (2014) study.

Furthermore, the proportion of controls with PLE (11.1%, n=38) was found to be broadly in keeping with published findings which have used the same methods to identify a subclinical group, i.e. participants endorsed one or more items on the PSQ (Bebbington & Nayani, 1995), excluding the hypomania questions, and including those who endorsed the first follow-up question about paranoia (Johns et al., 2004; Morgan et al., 2009). In a large national survey, Johns et al. (2004) found 5% of respondents (n=438) to report PLE using the method described above, and Morgan et al. (2009) found 18.3% (n=70) of individuals in southeast London to report subclinical psychotic experiences with this particular method. Other research has found that the prevalence of PLE, as measured by the PSQ, varies between 3.9% (Jenkins et al., 2010) and 19% (Tarricone et al., 2009) across different samples, and so it is perhaps not surprising to see some fluctuation between the results of this study and others which have used a similar method. Perhaps reassuringly, the proportion found in this thesis is an average of that found in the Johns et al. (2004) and Morgan et al. (2009) studies.

Selection bias can also arise as a result of drop-outs having different characteristics to the individuals who went on to complete full assessments. This possibility was checked in Chapter 5 by comparing the demographic characteristics of cases who completed the LEDS interview and for cases with missing LEDS assessments. Few notable differences were found between the cases who completed the LEDS and those who did not, and thus it is unlikely that any differences biased the findings of this study.

Further selection biases may have been introduced to the study through self-selection, i.e. the characteristics of individuals that make them more or less likely to take part in research. Certain psychotic symptoms e.g. paranoia, may have played a part in who agreed to take part in the study, and perhaps cases who were more unwell at the time would be less inclined to say yes and perhaps be more mistrustful of the purpose of this research. The experience of psychotic symptoms within controls may have also affected the recruitment and selection process. In particular, symptoms of paranoia might have made some individuals unwilling to answer the door to strangers or actively respond to an invitation to be part of a research project. Across both cases and controls, experiences of paranoia may have also made them more guarded about disclosing their experiences and unlikely to want to discuss experiences of adversity. However, if this effect on the reporting of life events was found to be systematically similar across cases and controls, then it would not affect the association, and therefore would not bias the estimate.

Other psychiatric symptoms, e.g. depressed mood, may also have made some cases, and also controls, less inclined, or able to take part. To try to reduce the possibility of symptoms affecting the potential cases who chose to take part in the research, the study researchers made sure they were available on the wards and in the community teams at regular times throughout the week to ensure individuals had the chance to enquire about the research on a number of occasions, and were given a number of opportunities to consider taking part.

The exposure under question, i.e. life events, may also have influenced who took part in the study and individuals who had recently experienced a severe event, e.g. death in the family, or birth of a child, may have been less likely to want to and/or be able to participate. The length of the assessment battery (up to five hours) may have also had an impact on self-selection and potentially lead to further selection bias. Although the total length of the interview was unlikely to be explicitly stated during the consenting process, potential participants were informed that the battery would be completed across two to three sessions, or as many as necessary. Therefore, there was some indication that the study carried a significant time commitment. This may have discouraged some individuals with attention or memory difficulties; a bias more likely to be seen in individuals with psychosis (Bora et al., 2010). However, this is only a problem if these individuals were also more or less likely to report exposure to recent life events and difficulties. Researchers tried to minimise the time burden from affecting the CECA and

LEDS assessments as these interviews were aimed to be completed during the first study appointment.

The impact of self-selection was considered in advance of study recruitment and various steps were taken to try to mitigate the effects of self-selection. These included compensating participants for their time with a small payment for taking part in the study, ensuring all participants were thoroughly briefed and felt comfortable about confidentiality and the purpose of the research, being flexible with regard to appointment times and lengths (e.g. steps were put in place to ensure individuals could be seen out of normal working hours and on weekends), and also where the appointment took place (e.g. home visits were conducted, and sessions booked at health centres before or after routine appointments). However, even with these steps in place, self-selection remains a complex issue, and the findings of this thesis must be cautiously interpreted in light of various potential biases.

Information bias

There are two forms of information bias: recall bias and observer bias. Recall bias can occur when the recall of a prior exposure is compromised by outcome status, e.g. by the disorder of interest. Observer bias can occur when the interviewer's knowledge of the outcome influences the way the exposure is assessed or classified.

Recall bias

Recall bias can affect case-control studies if the illness under study, e.g. psychosis, systematically increases or decreases the likelihood of recall of exposures, e.g. recent life events, relative to controls. A common criticism of case-control studies is that cases will be more likely to recall certain exposures in an 'effort after meaning', i.e. attempt to find answers which may help explain their current condition (i.e., why me, why now, etc.). Therefore, cases may be systematically more likely to recall exposure to life events, and arguably more negative events, than control subjects. Some researchers, such as Day et al. (1987), have argued that individuals with a first episode of psychosis may recall the experience of life events as occurring closer to onset than they actually did, as well as being more severe. In this study certain measures were put in place to try to minimise the possibility of 'effort after meaning' effects from biasing the results. In order to counter the first possibility, the researchers conducting the LEDS interviews

related life events to ‘anchoring points’ in the person’s history, including occurrences such as birthdays, religious festivals, instances of severe weather, etc. To counter the second possibility, all life events and difficulties rated using the LEDS were given a contextual rating which did not take account of the participant’s subjective view of the event’s severity. The fact that this study actually found greater numbers of overall events and difficulties reported by the control subjects goes against the possibility that cases were more likely to simply remember more events because they were searching for answers to questions about why they had become unwell.

Another possibility is that controls would be more likely than cases to recall events and difficulties because they only had to think back to their experiences over the past year. Contrary to the ‘effort after meaning’ effect described above, the effect of this possibility would minimise the chances of finding an association between life events and psychosis. Cases were questioned about their experiences in the year prior to onset, and for some individuals, this may have been a substantial period of time before the interview date (median length= 1.6 years, interquartile range= 1.3 years to 2.6 years prior to interview), and therefore cases may be more prone to forgetting events and difficulties. One way to overcome this is to restrict the case sample to only those individuals whose onset occurred recently, e.g. within the last month, to ensure that the recall period is as similar for cases as it is for controls. However, although this sounds promising in theory, in practice, it would be much harder to implement.

Firstly, if applied in this study, this restriction of cases to only include those whose onset was datable to within one month of interview would lead to a marked loss of power as only 15 cases had an onset that was very recent (i.e. less than one month prior to interview). Secondly, it is unclear how generalisable this would be to all cases with a first episode of psychosis. Systematic reviews on the duration of untreated psychosis (DUP), i.e. the time between the first onset of psychotic symptoms to the first contact with services/commencing antipsychotic treatment, vary considerably, with some finding an overall mean DUP of 124 weeks (Marshall et al., 2005), and others finding a much shorter median DUP of 9 weeks (Morgan et al., 2006). Taking note of these differences, it is clear that the distribution of DUP is heavily skewed, and within a first-episode sample there will be a proportion of individuals who have a more insidious onset, particularly individuals with schizophrenia (Morgan et al., 2006). Therefore, excluding these individuals with the purpose of reducing the impact of recall bias does

not seem like a sensible idea if our aim is to advance the overall aetiological understanding of psychosis.

Another way that recall bias may be reduced is to use alternative sources of information, e.g. from previous hospital records, or using an informant that knows the participant well. The use of informants was tested in the original study of life events and schizophrenia by Brown and Birley (1968) by asking patients and relatives about life events for the patient during the past three months. The authors found 81% agreement between patients and relatives, for whether or not particular life events had occurred, and further similar high levels of agreement (79%) have also been found in the seminal study of life events and depression (Brown & Harris, 1978). This high level of consistency, as well as the considerable practical and time constraints, led to the decision in this study not to seek external confirmation of life events and difficulties.

A more radical way to attempt to reduce recall bias is to disregard a retrospective approach and use a prospectively designed study instead. Some authors have argued that using a retrospective approach to assess the causal role of past exposures on later mental health outcomes, in this case, the influence of childhood adversity on later psychosis (Susser & Widom, 2012), is problematic and likely to overinflate the true association between these variables. The alternative would be to use a prospectively designed study, but a recent meta-analysis found similar findings across study designs and reports of early abuse collected prospectively and retrospectively were associated with similarly elevated rates of later psychosis (Varese et al., 2012). Similar findings have also been reported for more recent life events. Using a prospective study design, Wigman et al. (2011) reported a 3-fold increase in the odds of subclinical psychosis after exposure to recent adversity (OR=3.15). This finding is similar to what was found retrospectively in this thesis for psychotic disorder (OR=3.59), and in the meta-analysis of retrospective studies of disorder and psychotic experiences (OR=3.19), (Beards et al., 2013). Therefore, this consistency suggests that individuals with psychosis do not necessarily over-report experiences of adversity, which lends support to the collection of this information via a retrospective approach.

Observer bias

The second form of information bias which is pertinent in case-control studies is observer bias. This occurs when the interviewer's knowledge of the participant's

outcome status, i.e. whether they are a case or control, influences the way that they elicit information about prior exposures. This could occur by asking cases more leading questions or rating the participants' responses differently. More often, it is a subtler process whereby the interviewer will be more thorough about checking the presence of prior exposures in cases than they would be for control participants, consciously or not. Either way, this can introduce observer bias and threaten the integrity of the findings.

One way observer bias can be overcome is by 'blinding' the interviewer to the disease status under study. However, this is not possible when studying the influence of life events on the onset of psychosis, as the purpose of the LEDS interview requires researchers to specifically ask about experiences during a predefined period prior to onset (for cases) or interview (for controls). Furthermore, the researchers on this study were well aware of participants' outcome status due to the setting in which the cases were interviewed, i.e. on inpatient wards or at community mental health offices.

Although 'blinding' was beyond the scope of this particular project, the study did employ some techniques to try to minimise the impact of observer bias. The primary measure used for this thesis (LEDS) is a semi-structured interview, with the same standardised probe questions asked of every participant. The LEDS was rated according to clear coding guidelines and by following examples provided by the comprehensive manual. Additionally, all researchers received thorough training on this measure prior to commencing any interviews, and received regular refresher training throughout the course of the study. The authors of the measure- George Brown and Tirril Harris- were also available throughout the study period to advise on how to rate any ambiguous examples.

With the above techniques in place, it is still possible that observer bias may have occurred. To minimise this further, all researchers met for weekly consensus meetings to ensure the LEDS interviews were being rated consistently across the whole team, and to also eliminate any systematic errors being introduced by the same researcher. In addition, all of the LEDS ratings were thoroughly checked over the course of six months by the author of this thesis and at least one other member of staff, to ensure any errors in rating were corrected before the commencement of data entry.

8.2.2. Chance

In order to see if an observed result has occurred by chance, researchers make use of statistical testing and an assessment of confidence intervals. Case-control studies are advantageous in that they allow consideration of the impact of a variety of exposures. However, this also means that increasing the number of exposures increases the likelihood that an observed association arises through chance alone. Although traditionally the level of statistical significance is set at 95%, the p -value is a rather arbitrary determinant of what is significant and what is not, and this becomes more apparent when employing multiple tests. As multiple testing was common when looking at the characteristics of life events and difficulties on the odds of psychosis, as well as being apparent in the synergistic effects and mediation analyses, some of these analyses will have produced some positive findings where $p < 0.05$ by chance alone. Despite many odds ratios being tantalizingly large, the resulting confidence intervals were also very wide, which suggests many effects were not precise and were likely to be underpowered, despite the relatively large sample of cases and controls. With this in mind, it is advisable to be more cautious when interpreting findings where the $p > 0.01$, and it is recommended that these findings are replicated in much larger samples before more confident claims can be made.

8.2.3. Confounding

Confounding occurs when a third variable is independently associated with both the exposure and outcome under study and does not lie on the causal pathway. A confounding factor therefore provides an alternative explanation for an observed association. Strategies to address confounding in case-control studies can be applied during the design of a study and also at the analysis stage. During the design stage, the effects of confounding can be reduced through restriction, e.g. by excluding individuals with a known confounder, or by individually matching cases and controls on several key variables, or through sampling cases and controls to be broadly similar for a potential confounding factor, e.g. ensuring cases and controls contain the same percentage of male participants. More commonly, confounders are controlled for in the analysis stage, e.g. through stratification and regression analyses. Similarly to bias, confounding can lead to true associations being missed, as well as false associations being identified.

In this thesis, an attempt to control for potential confounding was made at the analysis stage through the use of stratification and logistic regression analyses. *A priori* variables (age, gender, ethnicity, social class), were identified based on factors which have shown previous independent associations with life events (exposure) and psychosis (outcome). Additional variables identified in the literature as further potential confounders in the relationship between life events and psychosis were added to a restricted sample of those with complete assessments, and these included cannabis use (e.g. Arseneault et al., 2002, 2004) and a family history of psychosis in first-degree relatives (e.g. Kendler et al., 1995; Miller et al., 2001). However, as a total of only 257 subjects completed assessments on drug use and family history (compared to the 554 subjects with complete LEDS assessments), some of these analyses were restricted by the reductions in power. There is also a further concern about the representativeness of these individuals who went on to complete these further assessments compared to those who dropped out. However, no marked attenuations in ORs were found after including these additional factors, and for the most part, overall interpretations remained the same.

It is important to note that there is no ‘test’ for confounding, i.e. there is no set amount or extent of confounding that should occur to be able to definitively say that a variable is or is not a confounder. Furthermore, including too many confounding factors in a model can undermine the precision of the estimate and possibly mean that a true association is overlooked (Susser et al., 2006). This is even more apparent when statistical power is low due to a limited sample size. Therefore, the number of confounders entered into the models in this thesis was kept to a minimum. All analyses were also presented as unadjusted and adjusted, in order to see the impact of correcting for the presence of potential confounders.

Furthermore, it is inevitable that even in the most rigorously designed studies, there will always be unidentified and unmeasured confounding factors which the researchers have not taken into account. Therefore, the stance should be taken that confounding is likely to have been underestimated, and the identification of further variables which may be of importance to these and similar analyses should be carefully considered by future studies.

Clinical variables which have not been included in these analyses, as the data was not available yet, include diagnosis, and severity and type of psychotic symptomatology. Previous research has found that specific types of events can have differential effects on different disorders, e.g. loss events are more commonly associated

with depression, and danger events with anxiety disorders (e.g. Finlay-Jones & Brown, 1981), whereas intrusive events are thought to be more specific for schizophrenia (Harris, 1987; Day, 1989; Harris, 1991), and goal-attainment events may trigger manic symptoms (Johnson, 2005). However, work within psychosis does suggest that an increase in marked life events three months prior to the onset of a psychotic episode is apparent, regardless of whether the psychotic diagnosis is one of schizophrenia, mania, or depressive psychosis (Bebbington et al., 1993). Furthermore, it has recently been suggested that diagnoses at first-episode should be considered provisional as only 59.6% of an incident first-episode sample were found to have the same baseline and lifetime ICD-10 diagnosis at a ten year follow-up review (Heslin et al., submitted). However, because the associations between life events and psychotic diagnoses/symptomatology have not been thoroughly tested within the literature to date, it is worth considering whether diagnosis and symptoms may affect the associations found between types of event and the onset of psychosis, and perhaps other characteristics of the life events data. Furthermore, longitudinal studies are likely to be needed in order to fully investigate this possibility.

8.2.4. Reverse causality

When using a case-control design, the possibility of reverse causality is difficult to rule out. Because the illness is already present when the cases are recruited, it becomes problematic to disprove that the illness was not responsible for causing the exposure to occur (or at least the reporting of the exposure). In order to minimise the possibility of reverse causation, researchers must be able to establish the temporal order of events. However, this is difficult in the field of social psychiatry especially when, for example, life events can perceivably arise as a result of illness-related behaviour.

To try to establish temporal ordering, the date of onset was measured as carefully as possible before the LEDS interview was conducted. Accuracy was increased by using a combination of participant interviews and thorough scanning of case notes, and by using a measure with established reliability and validity (NOS-DUP; Singh et al., 2005). Once the researcher was confident that the most accurate date of onset had been established, then the LEDS interview could be completed. At the beginning of the interview, the researcher would carefully explain that the interview would enquire about experiences which occurred for the one year period prior to onset

only, and this would be reiterated throughout the interview, with a timeline with notable anchor points being drawn to aid recall.

The independence scale within the LEDS measure also allows for the researcher to distinguish between events and difficulties which are unlikely to be the result of the disorder under study because their source was clearly 'independent' of the subject's agency (and therefore necessarily of any hypothetical developing symptomatology). Using this rating, if an association is found between independent events, difficulties and psychosis, then this can strengthen the *hypothesis* that these experiences may have a causal impact on the onset of psychosis, rather than being solely caused by characteristics of prodromal illness. This study found that there was an association with psychosis onset even when exposure to severe independent only events was considered. A similar effect was not found for independent difficulties but this is likely to be because so few of these experiences occurred for both cases and controls.

Within the confines of this particular study design, the temporal order of exposure and outcome were established as much as possible, although the possibility of reverse causality cannot be completely excluded. However, it should be noted that the issue of reverse causality is perhaps even more pertinent to the PLE analyses. Control participants were asked about the prevalence of various psychotic symptoms over the past year prior to interview in order to determine whether they met criteria for PLE status. However, these individuals were not asked for when these experiences began and therefore the lack of dating means that exposure to events and difficulties occurring before this date cannot be analysed exclusively. It is possible that some events and difficulties occurring across the year prior to interview happened after the onset of PLE, therefore limiting the possible proposal of a causal interpretation. Nonetheless, it is still important to assess the relationship of recent experiences and increased risk of PLE, as this information has important implications for prevention and intervention, and will also stimulate new ideas for future research directions.

8.2.5. Critique of the LEDS measure

Although the LEDS measure (Brown & Harris, 1989a) is widely viewed as the gold-standard measure of life events in epidemiological research by other prominent researchers in the field (Monroe, 2008), it is not without some limitations which are worth noting in the context of this discussion chapter. The major disadvantage of this

method compared with a self-report measure is the amount of resources and time that are needed for sufficient training (and re-training to maintain consistency), administration and rating. This can put burden on the researcher and adds to the cost of implementation, and some have argued that this approach is therefore not suitable for investigations that require large samples (Hammen, 2005; Dohrenwend, 2006). The extra expense required to facilitate regular consensus meetings has been viewed as a significant deterrent (Wethington et al., 1995). Furthermore, the fact that there is no limit to how many events and difficulties can be discussed during a LEDS interview, the burden for some participants can be higher than if they completed a self-report questionnaire (Katschnig, 1986). The LEDS also requires a level of self-disclosure that some participants (and also interviewers) might find uncomfortable (Wethington et al., 1995). Research into early traumatic experiences suggests that some participants may be too embarrassed to disclose life events in a face-to-face interview (Della Femina et al., 1990).

In the interest of advancing aetiological knowledge, there are also issues with comparability across studies. Only four studies to date have considered the relationship between life events and the onset of psychosis using the LEDS interview (Brown & Birley, 1968; Bebbington et al., 1993; Faravelli et al., 2007; Raune et al., 2009), and so a direct comparison between this thesis and other studies is very limited. This is an important issue to bear in mind, as although the resources were available to complete 554 LEDS interviews throughout the course of the CAPsy study, there is a real question about whether what was done will ever be replicated in future studies.

Psychotic disorders are also rare within the general population and many researchers look to advance the field through the use of large-scale studies of individuals with psychotic-like experiences. As these studies can contain samples of over 5000 adults (e.g. Johns et al., 2004; van Nierop et al., 2012), it is probably not feasible to use the LEDS measure to better understand relationships between life events and psychosis in these studies. However, it is worth noting that precise and reliable measurement can lead to large increases in statistical power, and so employing a more reliable investigator-based measure of life stress could reduce the required sample size needed to detect an association between life events and the disorder under study (Moffitt et al., 2005).

Another criticism of the LEDS approach, and of most investigator-based approaches to assessing life stress is the lack of consideration of subjectivity and

individuality, i.e. they do not take into account how the participant themselves views their experience of life events (Monroe, 2008). Although the contextual ratings of the LEDS system may sometimes mirror the subjective appraisal of an event, there will be instances in which the given threat rating may differ from the perspective expressed by the participant in the interview. As discussed in Chapter 2, proponents of an objective approach to measuring life events argue that the primary problem with subjective evaluations of events is that these can be affected by mood and mental state (i.e., by the very outcomes of interest) (Brown, 1974; Brown & Harris, 1989b), which would then risk confusing exposure and outcome and make it impossible to distinguish cause and effect. In an ideal study, both objective and subjective ratings of life events would be collected to see whether aetiological effects are driven by the way the individual views their experience, i.e. subjective appraisal, or by the objective environmental experience itself (Monroe & Kelly, 1995). However, other researchers have argued that subjective judgments are inappropriate in retrospective studies of illness as the participant is likely to attribute their illness to event(s) (Paykel, 2001).

Another key criticism of the LEDS approach is that the severity ratings may be confounded with socioeconomic status (SES) and other social vulnerability factors (Tennant et al., 1981; Dohrenwend, 2006). Although low SES may not define a threatening ongoing situation, researchers have argued that it is likely to be associated with severe life events, and therefore life events measures should be distinct from measures of other components of life stress processes (e.g. SES, personal predispositions, social support networks) (Dohrenwend, 2006). As the LEDS ratings procedure combines both situational and personal variables when deciding on an assessment of contextual threat, it has been argued that this combination makes it difficult to tell which factor may be responsible for a particular association between events and illness (Tennant et al., 1981; Kessler, 1997; Wethington et al., 1997). In order to combat the potential for confounding, Dohrenwend and colleagues devised the Structured Events Probe and Narrative Rating Method (SEPRATE; Dohrenwend et al., 1993). Before ratings are made, this measure places an emphasis on removing any demographic details from the life events narrative that may be of theoretical interest, so that raters are ‘blinded’ to these characteristics when making their decision about event severity (Stueve et al., 1998).

It is clear to see how there may be too much “context” included in the LEDS ratings of contextual threat when the example of a death event is considered

(Wethington et al., 1995). According to the LEDS guidelines, death ratings are influenced by factors such as the level of closeness to the individual, when they last had contact, and on the participant's support network. Therefore, the threat rating for death events can vary significantly and is heavily influenced by social vulnerability factors. However, the authors of the LEDS do argue that death is a more exaggerated example and that the majority of event and difficulty ratings are less influenced by social vulnerability, e.g. ratings of health events which are based more on objective features such as the expected prognosis (Brown & Harris, 1989a). Furthermore, it should also be noted that not all social vulnerabilities will be included in an event rating. Ratings are unlikely to take account of the vulnerability of being exposed to trauma in childhood, and many studies (including the CAPsy study) will measure this separately and analyse as an additional factor for the onset of illness (Wethington et al., 1995).

The generalisability of findings from LEDS studies have also been criticised by some researchers as they have mainly been undertaken in samples of women (Tennant & Bebbington, 1978). However, this criticism is perhaps only pertinent to the depression literature as the LEDS studies of life events and psychosis have contained varied samples of both men and women to date (Brown & Birley, 1968; Bebbington et al., 1993; Faravelli et al., 2007; Raune et al., 2009).

A further criticism connected to the LEDS approach that was the subject of much debate during the 1970s and 1980s, was the use of additive vs. multiplicative interaction models when studying the relationship between life events, vulnerability factors and depression. The debate began when Brown and Harris (1978) found that four vulnerability factors- maternal loss prior to 15 years, having three or more children under 14 years, lack of marital intimacy and lack of employment, contributed to the onset of depression, but only when combined with exposure to a stressful life event. The LEDS authors argued that these findings were evidence of synergy, or additive interaction (Brown & Harris, 1978). However, other researchers including Tennant and Bebbington did not share this viewpoint (Tennant & Bebbington, 1978; Bebbington, 1980; Bebbington et al., 1981; McKee & Vilhjalmsson, 1986). It was argued that the interaction found was model dependent as the use of an alternative multiplicative model failed to replicate the interaction finding (Tennant & Bebbington, 1978; McKee & Vilhjalmsson, 1986). At that point in time, an additive model was not as favoured by statisticians as was a multiplicative model (e.g. Everitt & Smith, 1979; Costello, 1982). However, this viewpoint has shifted considerably over the past few decades, and the

critical issue here is that a case can be made for using both approaches. The key is that the choice and rationale needs specifying *a priori*. However, many researchers do now consider an additive model to provide the best representation of the combined effect of two variables (Rothman et al. 1980; Schwartz, 2006; Kendler & Gardner, 2010). Indeed, that is the approach chosen by this thesis to model interactions between life events, negative schemas, social class and psychosis, and it has also been recently adopted when considering associations between childhood trauma, life events, cannabis and psychosis (Morgan et al., 2014).

However despite its limitations, research has shown that the use of the LEDS approach is likely to give a much more detailed and accurate overview of recent events compared with a checklist method. For example, a study by McQuaid et al. (1992) found that only 38.5% of life events reported with a self-report checklist corresponded with events elicited by a LEDS interview. More recent studies also suggest a large discrepancy between interview and checklist methods. Duggal et al. (2000) found that a self-report measure captured only 32% of severe events and 36% of major difficulties identified by the LEDS in those with a first episode of major depression. Lewinsohn et al. (2003) found that the overall percentage of checklist events also found by the life events interview was below 50%. Researchers suggest that the comprehensive nature of the LEDS interview (Brown & Harris, 1989a), and the potential for an increased rapport between the participant and interviewer, may allow for more events and difficulties to be more readily and reliably uncovered (Blaney, 1986). It has been estimated that participants can reliably report on exposure to severe life events for up to ten years using the LEDS system (Neilson et al., 1989). Although less severe events may not be so reliably recalled over a longer timeframe (Brewin et al. 1993; Hardt & Rutter, 2004). The fact that the LEDS method allows for further probing means that the threshold for inclusion of an event is higher than for a checklist interview. A major problem with checklists is that participants can interpret the same life event descriptor in many different ways and there is a risk of misclassifying a relatively banal experience as one which is more serious (Dohrenwend, 2006; Monroe, 2008). Therefore, checklists are likely to contain a higher proportion of relatively minor incidents, many of which would not meet the inclusion criteria for what constitutes a life event, as assessed by an interview measure (Dohrenwend, 2006).

One of the key criticisms of any life events measure used in epidemiological research – be it a checklist or interview, is that people who are already unwell may be

more prone to endorse the occurrence of life events and difficulties in an attempt to seek an explanation for the occurrence of their disorder (Brown, 1974). This bias can lead to systematic errors and encourage spurious associations between life events and illness. However, if researchers favour the use of a checklist measure rather than an interview, then there is no means for the participant to clarify the question, or provide the interviewer with more contextual details which would enable a decision on whether the event meets the threshold for inclusion (Schwartz, 2007). Therefore, one of the main attractions of a checklist approach for life events- i.e. its expediency and low interviewer burden, may also contribute to a major limitation of this method (Monroe, 2008). Furthermore, in the case of aetiological research, where the extraction of precise timings for onset and pre-onset events is required, more intensive questioning and assistance as afforded by a life events interview could be argued to be essential in this context (Duggal et al., 2000; Monroe, 2008). The nature of the face-to-face interview with the addition of qualitative probes, visual timelines, and reminders of salient dates, all play a key role in improving event recall and accurate dating (Wethington et al., 1995). Precise dating, as aided by an approach such as the LEDS (Brown & Harris, 1989a), is necessary not only to establish the relationship of life events to onset, but also to help identify aspects of the experiences that may have influenced onset, and therefore is an essential part of a successful aetiological study.

8.3. Interpreting the findings

Having acknowledged the main methodological limitations of the present study and also highlighted the ways in which these have tried to be addressed, the focus will now shift back to the findings themselves and to integrating them with the literature to date. This section will firstly recap on the main original contributions of the thesis and will then go through some of the main themes in relation to the previous literature, including the characteristics of recent experiences prior to psychosis onset, demographic interactions, and synergistic and mediation effects of social class, schemas and affective symptoms.

To reiterate some of the key original contributions of this thesis, this study is the first to explore the prevalence and impact of recent life events and difficulties in an epidemiologically-derived sample of first-presentation psychosis patients compared with an unaffected control group. Furthermore, it is the largest case-control study to use the comprehensive, gold-standard measure of life events and difficulties, the LEDS, to

explore the role of recent life events and difficulties, and also the first to use this in-depth measure to assess the impact of recent experiences on psychotic-like experiences within the general population. To date, there have also been no studies which have considered the impact of severe difficulties on the aetiology of psychosis, and as this thesis considered the same analyses for both events and difficulties, these findings contribute to advancing our understanding of the impact of more long-term stressful exposures. In terms of synergistic effects, this study is the first to assess whether there is an additive interaction between low social class and life events/difficulties. This thesis is also the first study to investigate the interaction between negative core schemas and threatening life events/difficulties in discriminating between cases with psychosis, controls with PLE and controls without PLE. Furthermore, pathways from adverse adult experiences to psychotic disorder, via affective processes, have yet to be explored.

8.3.1. Characteristics of recent experiences prior to psychosis onset

Severity

One of the key findings to come out of this thesis is the importance of taking event/difficulty severity into account when considering the aetiological impact on psychotic disorder. In this study when severity was not considered, no associations were found between exposure to life events and difficulties and an increase in the odds of disorder, and control subjects even showed an increased number of life events overall. It seems that only events and difficulties with an appreciable level of threat were acting to provoke a first episode of psychosis, with a three-fold increase in odds found for severe events, and roughly a five-fold increase in odds after exposure to severe difficulties. These relationships were also found to be very robust, and the strong statistical significance of the findings were in no way reduced by controlling for *a priori* demographic variables (age, gender, ethnicity, social class), and the additional confounders of current cannabis use and family history of psychosis.

In terms of comparability, these findings of the importance of severity do support many previous findings within the literature. The two other first-episode studies which have also used the LEDS found similarly large increases in moderate and severe life events three months prior to onset in cases compared with controls (Faravelli et al. 2007, OR=3.2; Raune et al., 2009, OR=5.0). The seminal study of Brown and Birley

(1968) also reported that the excess of events is particularly apparent for the more serious examples. However, although Bebbington et al. (1993) found that an excess of pre-onset events was more evident for severe events, they did also see associations for events with relatively mild threat. Many previous studies have found that the percentage of cases exposed to severe events prior to onset is roughly 50%, which is similar to the figure (48.6%) found in this thesis. Previous studies of life events and psychosis have found the following percentage of cases to report recent severe life events prior to the onset of symptoms: 46% (Brown & Birley, 1968), 61% (Canton & Fraccon, 1985), 52% (Bebbington et al., 1993), and 51% (van Os et al., 1994).

This thesis also found evidence for a cumulative increase in odds of psychosis with an increasing number of severe events and difficulties experienced. This is in keeping with the literature on trauma and psychosis. For example, a large community study found that experiencing two or more trauma types was associated with psychosis, and there was evidence of a dose-response type relationship (Shevlin et al., 2008). A potential cumulative impact of recent life events has also been found in relation to odds of PLE in a large community sample. Morgan et al. (2014) reported very strong evidence of a linear relationship between the number of events experienced in the past year and the odds of psychotic experiences. Although it was expected that a similar pattern would be found for severe cumulative experiences in this thesis, the number of controls with PLE who reported severe events and difficulties was too small to permit any analyses of cumulative effects.

Potentially due to small numbers and sampling error, there was no evidence of an association between severe life events and PLE, although an association was found for severe difficulties. However, it is not thought that there is a differential effect for an association between difficulties and PLE, and not for events and PLE, as the numbers of controls with PLE who were exposed to severe events was greater than for controls without PLE. These effects are in the hypothesised direction but low power may be limiting a conventionally significant association from being found.

To conclude the discussion of the impact of severity, it should also be pointed out that, although serious, these events grouped together as ‘severe’ are on the whole of everyday quality, rather than being catastrophic and likely to induce a PTSD reaction. Such events are common in the general population and experienced by many individuals across the course of everyday life. Few of the severe events and difficulties are likely to be major crises such as death or life-threatening illnesses, but rather more

commonly experienced disturbances such as marital and relationship breakdowns, redundancies and interpersonal arguments. Because these experiences are common, and perhaps will become even more prevalent over the years to come with recent increases seen for exposures such as economic instability, unemployment, and divorce rates; therefore the clinical implications of these experiences must be taken seriously (Corcoran & Nagar, 2010; Ceccherini-Nelli & Priebe, 2011).

Intrusiveness

Despite the intrusiveness hypothesis being first proposed nearly thirty years ago (Harris, 1987; Day, 1989; Harris, 1991), the search for particular types of adult life events that may trigger a first episode of psychosis has been relatively neglected. The present study did find strong evidence that intrusive events and difficulties were common prior to a first episode of psychotic disorder. Intrusive events were found to be associated with a six-fold increased odds of psychosis and intrusive difficulties were associated with around a twelve-fold increased odds of disorder.

In terms of previous literature, Raune et al. (2009) found that exposure to intrusive events in the three months prior to onset appeared to increase the odds of psychosis by seventeen times. However, this study is limited by the use of the control subjects being from a study conducted 20 years previously. Other than the Raune et al. (2009) study, and the reanalysis of the Brown and Birley (1968) study by Harris (1991), the impact of intrusive life events in adulthood on the onset of first-episode psychosis has not been thoroughly investigated, despite researchers hypothesising their potential aetiological importance (Harris, 1987; Day, 1989; Harris, 1991).

In this thesis, exposure to intrusive difficulties was also found to be elevated for controls with PLE compared to controls without PLE. Although these findings were presented as exploratory, they do fit with a previous study of adolescents with schizotypal personality disorder (SPD) and proposed to be at risk of developing a later schizophrenia-spectrum disorder (Tessner et al., 2011). Individuals with SPD were found to report a greater number of experiences associated with criminal and legal activity, compared with individuals with no psychiatric symptoms. The types of events and difficulties experienced clearly had an intrusive element and examples included being assaulted or robbed, involvement in a lawsuit, and being arrested and sent to prison. More recently, a large general population study also found that exposure to

intrusive life events in the past year was particularly associated with an increased likelihood of endorsing psychotic experiences (Morgan et al., 2014).

The concept of intrusiveness clearly has some relevance to psychosis as it fits conceptually with the types of experiences that have been found to increase the risk of psychosis, e.g. sexual abuse (e.g. Spataro et al., 2004; Cutajar et al., 2010; Bebbington et al., 2011), severe bullying (e.g. Kelleher et al., 2008; Arseneault et al., 2010; Trotta et al., 2013; Takizawa, Maughan, Arseneault, 2014), military combat (e.g. Steinberg & Durrell, 1968; Beighley et al., 1992), and high expressed emotion (e.g. Vaughn & Leff, 1976; Bachman et al., 2002), and so it is perhaps not surprising that such strong associations were found between intrusive life events and difficulties and psychosis in this thesis. However, it is also important to stress that without looking at other event themes, e.g. loss, danger, humiliation, we cannot know whether experiences which are intrusive are more likely to be associated with psychosis. Although the evidence suggested by this thesis is compelling, further studies are required which test the impact of other stress dimensions in order to properly test the specificity of intrusiveness.

Independence

In order to see whether experiences which were out of an individual's control could influence associations with psychosis and give some insight as to whether the occurrence of a life event or difficulty may be a cause of psychosis, the effect of independence was considered. Although exposure to possibly dependent events was associated with greater increase in odds, exposure to independent life events was still found to be associated with a three-fold increased odds of psychosis, and this supports many earlier research findings (e.g. Brown & Birley, 1968; Ventura et al., 1989; Bebbington et al., 1993; Faravelli et al., 2007; Raune et al., 2009). No effects were found for independent difficulties but this is probably because so few difficulties of a severe nature were classed as independent. In fact, other than very severe health problems affecting a close friend or relative, it is difficult to think of any severe difficulties which would be rated as being outside of an individual's control.

Overall, the fact that associations were generally found for both independent and possibly dependent experiences suggests that the onset of psychosis may be triggered both by the experience of random severe events, which are completely outside of an individual's control, but also that individuals susceptible to psychosis may generate

their own life stress, either as a result of prodromal symptoms and/or personality characteristics. Early symptoms of an emerging psychosis, such as irritability and withdrawal, may contribute to the occurrence of some events, e.g. interpersonal difficulties and problems at work. It is therefore plausible to see that as an individual possibly begins to lose friendships and work opportunities as a result of their behaviour, this may increase feelings of depression, anxiety and paranoia, and may potentially spiral into a psychotic episode further down the line. In other words, it is not simply that events are either a cause or consequence of (emerging) psychosis; each may compound the other, creating a vicious circle that, over time, pushes some along pathways to later psychotic disorder.

Although it is helpful to assess the presence of independent experiences in a bid to understand possible causation and direction of effect, it is perhaps more pertinent to understand the role of possibly dependent experiences if we want to improve preventative efforts. Exposure to random and independent experiences cannot be controlled, but the way that individuals contribute to the occurrence of certain events and difficulties, as well as the way they react to them, is something that can be studied in order to improve later health outcomes.

Focus

By definition, severe events and difficulties will be more than likely to involve the subject in a direct way, and therefore it is no surprise that as severe experiences were found to be strongly associated with psychosis in this thesis, the odds of psychosis after exposure to subject focused events was slightly higher than for other types of focus. A four-fold increase in odds was found for exposure to severe events, whereas exposure to joint and other-focused events increased the odds by just under two-fold. A similar pattern was seen for difficulties but with slightly more pronounced effects.

The findings of this thesis fit the limited previous literature into this particular characteristic. Brown and Harris (1989b) found that only severe events which were also focused on the subject were found to be associated with an increased risk of depression. Other more recent studies of depression have also confirmed a role of subject focused events, although this study looked at non-severe events only (Monroe et al., 2006). Although there are no other published studies which have assessed the impact of event focus on the onset of psychosis, it is plausible that experiences which have a direct

impact on, or a direct meaning for the subject, could create feelings of being targeting and singled out, thus increasing the risk for paranoia and further psychotic symptoms.

Timing

Although this thesis did find some support for the contention that life events have a triggering role in the onset of psychosis (Brown & Birley, 1968; Day et al., 1987), with a preponderance of events found in the final three weeks prior to onset, the wide confidence intervals suggest that this effect is not precise and the possibility that this finding arose out of chance cannot be excluded. Furthermore, the fact that exposure to severe events appeared to be associated with similar increases in the odds of psychosis across the final three quarters of the year prior to onset suggests a more likely explanation is that events have a cumulative effect over a period perhaps as long as nine months prior to the onset of psychosis. Brown and Birley (1968) also reported that 70% of those found to have experienced a life event prior to the onset of symptoms had also experienced an event in a previous three week period, which indicates that there may be an additive role for life events. Therefore, there is not necessarily a dichotomy between an increased rate in the final three weeks prior to onset and an overall increased rate of events across the follow-up period under study. Interestingly though, no differences were found between cases and controls for the first three months furthest away from onset/interview which does suggest some influence of timing effects. It is likely that the experience of severe events closest to onset, albeit up to nine months pre-onset, which are most important in terms of aetiology.

Duration of difficulties

A consideration that has not been investigated within the psychosis literature is the impact of chronic difficulties on the onset of disorder. Although the LEDS probes for this information, to our knowledge, no study so far has investigated this in individuals with psychosis and only a few studies have looked into this in depressive illnesses (e.g. Brown et al., 1986; Brown & Moran, 1994; Brown et al., 1994; Farmer & McGuffin, 2003; Husain et al., 2012; Traviss et al., 2013). Although it makes intuitive sense that difficulties of a longer duration would have more of an impact than those which were resolved more quickly, this thesis did not find evidence to suggest that longer difficulties exert any more of an impact on the odds of psychosis than difficulties

which lasted less than six months. Currently, it remains unclear whether severe difficulties of a longer duration are more likely to be associated with an increase in psychosis over difficulties of a shorter duration.

Links to symptom severity

An investigation of the impact of pre-onset events and difficulties on general psychopathology symptom severity in individuals with psychosis has yet to be explored in the literature, and so the link to symptom analyses were presented as exploratory. Although it has been proposed that an event-related onset may be more likely to be initially associated with more florid symptoms and then a more benign course (e.g. van Os et al., 1994, 1998), than those whose onset of illness was not preceded by stress, this was not confirmed by the findings of this study as there were no differences in general symptom severity between those who reported being exposed and not exposed to severe events one year prior to onset. Furthermore, these results also provide some counter evidence for the claims that individuals with psychosis are more prone to reporting exposure to stressful experiences as they may be confused or detached from reality (Lysaker et al., 2005). Although associations were not found in this study between overall symptom severity and exposure to severe experiences, there may still be differences in terms specific exposures and individual symptoms, e.g. those reporting exposure to intrusive experiences may be more likely to also report symptoms of paranoia.

However although an association between stressful experiences and symptom severity was not found in this study, associations with stress and GAF symptoms have previously been found in relation to perceived stress. Renwick et al. (2009) found overall GAF symptoms and depression symptoms to be highly inversely correlated with perceived stress in patients with a first-presentation of psychosis. Although, as perceived stress is a subjective assessment of recent stress exposure which may be heavily influenced by mood, this makes it very difficult to disentangle cause and effect. Furthermore, 70% of the participants in this study were hospitalised which is likely to play a role in increased symptom scores and also perceived stress levels (Renwick et al., 2009). Other studies have found that when patients have been prospectively followed up, there is evidence to suggest that the occurrence of daily hassles is related to increased symptom severity in individuals with psychosis (Norman & Malla, 1994).

Another potential limitation of this study is that the GAF symptom data only covered the month prior to the study assessment. Therefore, there is no account of the severity of symptoms prior to this period or the persistence of symptoms across time. In terms of interpreting the findings of this thesis, perhaps too much time has passed since onset (median length of time = 1.6 years) in order to see an appreciable difference between those exposed and not exposed to recent stressors, and an association with symptoms may have been more likely if the patients were assessed at the point of onset.

Another mechanism which may also influence associations between life events and psychotic symptoms is that of stress sensitivity. A study by Docherty et al. (2009) found that life events only led to increases in symptom levels in patients who were most emotionally reactive to stress. Therefore, it may be that a heightened sensitivity to stress which is driving the pathogenic effect of environmental stress. There is a whole body of evidence which supports an association between increased stress sensitivity (Myin-Germeys et al., 2001, 2003; Myin-Germeys & van Os, 2007; Lataster et al., 2009), and it would be interesting to further consider the associations between objective life event ratings, stress sensitivity and specific psychotic symptoms in future studies.

8.3.2. Group variations in effect

Gender

Against what was hypothesised and many previous research findings (e.g. van Os et al., 1994; Myin-Germeys et al., 2004; Gibson et al., 2014), the association between severe life events and psychosis was found to be greater for men than it was for women. Although previous research suggests the risk of mental illness is greater for women after exposure to severe trauma, men have been found to experience more traumatic events overall, and especially exposure to more physical assaults and violence across the lifetime (Kessler et al., 1995). These types of experiences are what would be classed as intrusive, and therefore this could explain the gender differences as intrusive experiences were found to be highly associated with psychosis in this sample. One way to test this theory would be to see whether gender differences were seen when considering intrusive events and difficulties across the different strata. However, this study did not find any significant gender effects but this is likely to be an effect of small

numbers when narrowing down to look at the particular characteristic, in combination with severity.

To further complicate the picture, the gender effects seen for severe events were not replicated for severe difficulties. Compared to severe events, women were more likely to be exposed to severe difficulties (events experienced by 48.5% of female cases and difficulties experienced by 65% of female cases), whereas the proportion of male cases exposed to severe events vs. severe difficulties was roughly the same. Therefore, this increase in women experiencing severe difficulties could explain why a gender effect was seen for events but not for difficulties. Women may be more likely than men to report exposure to specific severe difficulties involved with the traditional caregiver role, e.g. difficulties returning to work after having children, difficulties of being a single mother, having responsibility for looking after children and elderly relatives. This increase in difficulties for women was seen for both cases and controls, albeit more pronounced in cases.

Age

An effect of age was found for both severe events and difficulties, with associations with psychosis being found to be stronger for those under 30 years compared with those over 30 years. Older controls were more likely to report exposure to both severe events and difficulties, whereas exposure to severe events and difficulties was roughly equally distributed across the two strata for case subjects. These age effects could be partially explained by the types of experiences reported by the cases and controls. For controls, the most common type of severe event and difficulty experienced concerned health, and all other domain types fell far behind. It may be that severe experiences relating to health increase with age, which would explain some of the age effects in controls; whereas, cases were likely to experience severe events and difficulties of multiple types, which perhaps cut across the age groups more than health related experiences. There was tentative evidence of a weak effect of age on intrusive experiences, whereby the odds of psychosis after exposure to severe and intrusive experiences were higher among those under 30 years.

Despite reasonable sample sizes for both cases and controls, a large number of analyses were performed on this data. This is especially true for the interaction analyses,

where the smaller sub-samples could have influenced the possibility of spurious associations. Power was severely limited for these analyses, and therefore these findings should be interpreted with great caution and these investigations require testing in much larger epidemiological samples.

8.3.3. Synergistic effects of social class, schemas and affective symptoms

Lower social class as a causal partner?

It has long been acknowledged that there are associations between lower social class, experiences of adversity and mental illness (e.g. Cooper, 1961; Brown & Harris, 1978; Marmot, 2004; Weich & Lewis, 1998; Lorant et al., 2007). To our knowledge, this thesis is the first to test whether low SES and severe events/difficulties act synergistically to increase the odds of psychosis. The analysis found independent effects of low SES, and exposure to severe events and difficulties, but when these factors were present in combination, the odds of psychosis were especially large, albeit with very large confidence intervals. This interaction found between SES and severe experiences may have come about because class is a proxy for access to resources and therefore, both the lack of resources and events/difficulties together compound the effects of each alone (Szaflarski, 2006). Although replication is required in other studies, these findings tentatively suggest that individuals with low SES are more at risk of psychosis when they experience misfortune in adulthood compared with individuals from higher social classes.

Ways to potentially target social class include improving education and employment opportunities, and more broadly, to redistribute wealth and reduce inequality. There is a move to improve the education and future employment opportunities of young people as currently in England, the minimum age at which young people can leave school is being increased. As of summer 2013, young people were required to continue in education or training to the end of the academic year in which they turn 17, and from next summer 2015, they will be required to stay in either full-time education, an apprenticeship, or full-time employment or volunteering plus part-time accredited learning, until their 18th birthday. This major overhaul of the education system is expected to benefit future generations and improve their quality of life, and this may go some way to increase an individual's social class from that of their

parents. Furthermore, these changes are likely to have other knock-on effects, including potentially having an impact on juvenile crime rates, as a recent review paper suggests that a minimum dropout age can have a significant and negative effect on property and violent crime arrest rates for individuals ages 16-18 years (Anderson, 2014).

Negative schemas as a causal partner?

Negative schemas are thought to underlie the mistrust and suspiciousness which leads to the development and maintenance of positive psychotic symptomatology. They have been found to be present in both subclinical psychotic experiences and psychotic disorder (Fowler et al., 2006b), and have been theorised to combine with experiences of life events and difficulties to increase the risk of disorder (Garety et al., 2001, 2007). As hypothesised, cases were found to have both higher levels of negative self-schemas and negative other-schemas compared with controls. Furthermore, these differences were also seen between controls with PLE and controls without PLE, which suggests that these negative schemas may be a marker of risk for later psychosis.

In the literature to date, there have been no known investigations of the potential synergistic effects of negative core schemas and recent stressful experiences on increasing the odds for psychotic disorder. Studies to date have only considered this factor as a potential mediator of the relationship between traumatic experiences and later subclinical psychotic experiences within general population samples (Gracie et al., 2007; Fisher et al., 2012; Freeman et al., 2013). Interestingly, this study found evidence of independent effects of both negative self- and other-schemas and independent effects of severe life events and difficulties on increasing odds of psychosis, but it was when these variables came together, that increasingly large associations were seen. Although these findings must be cautiously interpreted, there was weak evidence to suggest a synergistic effect of negative self-schemas in the relationship between severe life events and psychotic disorder, and a similar effect found for negative self-schemas, severe difficulties and psychotic disorder. Furthermore, there was also suggestive evidence that these processes increase the odds of PLE within the control sample, although all of the PLE synergistic analyses were weakened by the small numbers in this group. Although these findings have clear implications for treatment, they nevertheless require replication in much larger samples.

However, surprisingly what was not found was evidence of an additive interaction between negative other-schemas and severe events/difficulties in increasing odds for psychotic disorder. A possible explanation for this finding could be due to the distribution of affective and paranoid symptoms throughout this particular sample. It may be that if the cases have an abundance of individuals with a more affective psychosis, that their rates of negative self-schemas would be greater than for individuals with a predominately paranoia-driven illness. Another explanation could be that negative-other schemas are more common in controls, and it is quite conceivable that individuals living in inner London would be more likely to have an increased level of general mistrust than in other parts of the country. When looking at the breakdown of each strata in the synergistic analyses, cases and controls were found to have similar proportions of those with negative other-schemas only. However, this was also found to be the case for negative self-schemas. Possibly the precursors to psychosis are more affective than what has previously been thought, and these findings tentatively suggest a more affective, depressive pathway to psychosis.

Affective symptoms as mediators?

Before assessing the role of affective symptoms as potential mediators between severe pre-onset experiences and psychosis, the level of depression and anxiety at the time of interview was compared between cases and controls. It was found that both increased levels of anxiety and depression were associated with increased odds of psychosis. This is in line with previous literature which has found increased levels of affective symptoms to be frequently co-morbid with psychotic disorders (Smith et al., 2006; Freeman, 2007; Bentall et al., 2008; Freeman & Fowler, 2009). Furthermore, increased levels of affective symptoms were also found to be present in the controls with PLE compared to controls without PLE. Similar to research into psychotic disorder, these findings also mirror the previous literature as affective symptoms have been found to frequently be present during the initial prodrome of psychosis (Hafner et al., 1999).

In the literature to date, there has yet to be an investigation of the potential pathways from threatening life events and difficulties, to psychosis onset/subclinical symptoms via anxiety and depression. In previous studies, the pathway between adversity and psychosis via affect has mainly been tested in general population samples (Freeman & Fowler, 2009; Fisher et al., 2012). Furthermore, in those studies that have

considered clinical disorder, only pathways from early adversity to psychosis have been considered (Bebbington et al., 2011; Fisher et al., 2013a).

Against what was hypothesised, this study did not find any convincing evidence that affective symptoms mediated the association between life events/difficulties and psychosis. A simple explanation for the lack of a mediation effect is down to the sample size as previous studies have found positive effects with samples of on average 7000 participants (Bebbington et al., 2011; Fisher et al., 2012). However, initial power calculations indicated that this sample was large enough to detect evidence of mediation. It was estimated that with a sample of 400 (mediation sample was eventually 471 subjects), using a conservative rule allowing for one parameter for every 20 subjects, this would allow up to 20 variables to be entered into a mediation model. Only eight variables were entered into the mediation models (exposure to either life events or difficulties, case or PLE status, two mediators of anxiety and depression, and four confounders of age, gender, ethnicity and social class), and so there was adequate power to detect a mediation effect.

Another important consideration is that the measurement of affective symptoms was taken at the time of the assessment and not closer to the date of the severe experiences, when emotional reactions were likely to have been more pronounced. Furthermore, as the outcome and mediator were assessed at the same time, there is no temporal ordering and so we cannot confidently say that these variables lie on a causal path to psychosis. However, levels of negative affect have been found to be reasonably stable across the course of schizophrenia (Horan et al., 2008), and so measuring the level of affective symptoms at the time of interview is unlikely to have considerably weakened the potential mediation effects.

Despite there being evidence that adverse life events are associated with increases in anxiety and depression (e.g. Ventura et al., 2000; Fowler et al., 2006a), and these symptoms also being associated with the later development of psychosis (e.g. Krabbendam et al., 2005; Freeman et al., 2011), there was no substantial evidence of mediation via affective symptoms in this study and it is clear that other factors are likely to lie on the causal pathway between life events, difficulties and psychosis.

8.4. Clinical Implications

In order to discuss the implications of this thesis for the treatment and prevention of psychosis, I will return back to the quote stated at the start of the introductory chapter, and consider which parts of the causal chain can be potentially broken or modified. From the findings of this thesis, the key areas to focus on are supporting people to minimise exposure to potentially preventable life events and difficulties, providing improved opportunities for support and access to resources after a severe event or difficulty has occurred, and reducing negative core beliefs about the self, ideally from an early age. As life events/difficulties, low SES and negative beliefs have been found to combine synergistically to increase the odds of psychosis, these associations tell us something about who is most likely to be at risk, and can enable us to target certain groups. It also means that removing one of these causal partners will, in theory, be enough to break the causal chain.

However to start off with, it should be clearly stated that the results of this thesis are not suggesting that exposure to severe life events and difficulties are either necessary or sufficient for the onset of psychosis. Roughly half of the cases experienced severe life events and difficulties prior to the onset of their disorder, with the other half experiencing onset without recent exposure to a severe event/difficulty. Similarly, around a fifth of control subjects experienced severe life events and difficulties without displaying any signs of psychotic disorder. That being said, if a focus on minimising the impact of adverse experiences in adulthood could potentially help around half of the individuals who will develop psychosis, then this could go a long way to prevent and also better manage this disorder.

This section will now continue with an overview of how the findings of this thesis could potentially improve preventative efforts, and then how they could be used to improve assessment and treatment in those who have already transitioned to psychosis.

Preventative efforts

Unfortunately, social adversity has been found to cluster within individuals and persist over time (Pantazis et al., 2006), with evidence of prolonged and cumulative exposure (van Os, Kenis & Rutten, 2010). The effect of childhood adversity may both predict later adversity in adulthood, and also interact with adult adversity to increase the

risk of developing psychosis (Lataster et al., 2012; Morgan et al., 2013; 2014). Furthermore, childhood adversity, negative schemas and adult adversity are likely to be very much interlinked as childhood trauma has also been found to increase negative schemas about the self (Fisher et al., 2012), and the evidence from this thesis suggests that negative self-schemas and adult life events combine to increase the odds of psychosis. Therefore, if the deleterious effects of adult life events depend, for some, on prior exposure to trauma in childhood, then focusing preventative efforts on reducing, or more likely minimising, the negative effects of childhood trauma is a key priority.

One preventative strategy could be to target those who have been exposed to childhood adversity in an attempt to help them better cope with their experiences and reduce the likelihood of further victimisation and later mental ill-health. Research has found beneficial effects of CBT in children who have been sexually abused, with later reductions in PTSD symptoms and other mental health problems (Ramchandani & Jones, 2003). Positive findings have also been found for enhanced foster care schemes for chronically maltreated children (Kessler et al., 2008). Early intervention is key as effective treatment in childhood and adolescence can lead to significant reductions in mental health problems in adulthood (Kim-Cohen et al., 2003).

Preventative efforts have also been focused on those considered to be at risk for developing psychosis. Psychological interventions, such as CBT, have shown some promise (Morrison et al., 2004; Cannon et al., 2008), and have been used to help prevent exposure to or minimise the consequences of adverse experiences. Other cognitive training techniques, such as cognitive bias modification (CBM), may also be helpful and these aim to reduce negative biases and decrease selective attention to threat-related stimuli (Hertel & Mathews, 2011). These techniques can be taught to individuals at risk of disorder, but also within the general population, in order to help reduce maladaptive reactions to everyday stressors. A recent study found that five sessions of online CBM reduced social anxiety in young adults about to start university, and showed some promise as a preventative tool to help reduce negative anxiety in relation to challenging and upcoming life events (Hoppitt et al., 2014). As anxiety is often co-morbid in those at-risk for psychosis (Salokangas et al., 2012), these cognitive techniques may also show promise for preventing psychosis, although this is yet to be studied in an at-risk sample.

Improving assessment and treatment

An appreciation of the impact of life events on psychosis onset could also be an important discussion point in therapy sessions for individuals who already have psychosis. The results of this thesis support the view that psychosis should be understood within the context of a person's biographical history and current social circumstances (Fowler, 2000), as recent exposure to psychosocial stress will often be an antecedent factor in a first episode of illness. Early therapeutic work which discusses the impact of recent adverse experiences may help to normalise the experiences of psychosis as understandable reactions to life events (Gamble & Brennan, 2006), while pointing the way to therapies targeted at specific symptoms and specific psychological processes.

Making links between psychosis and the person's life experiences can improve the power of the clinical formation and is likely to be more acceptable to patients than the explanation that they are simply 'ill' as this is not something which is within their control (Tait et al., 2010). A cognitive re-assessment of recent severe experiences may help to reduce catastrophic and categorical thinking, and relapse-prevention work might focus on planning how the person would cope with any future, potentially paranoia-inducing, intrusive experiences (Tait et al., 2002).

The prevalence and pattern of severe life events before psychosis onset underlines the importance of the social environment for the person recovering from psychosis. It therefore supports the use of early intervention using a standard stress management component and supporting individuals to minimise the occurrence of 'possibly dependent' events is an important clinical aim. Psychological therapy could also be used to disentangle which events were independent of the person themselves, which were possibly caused by the person but not the illness, and what might be related to illness characteristics. Timelines have also been used in therapy sessions which enable the patient and the mental health worker to clarify the occurrence of adverse events and reactions so that an improved understanding of these risk factors can be a learning experience (Ford, 2000; Marland et al., 2011). This may help an individual with a first episode of psychosis to have a more realistic interpretation of the role of both external stress and the role of personal vulnerabilities in the onset and management of psychotic symptoms (Ford, 2000). Furthermore, timelines can also be a useful tool to highlight evidence of resilience (Brabban, 2009), and this may empower the individual to feel that they could cope with further adversity if it arose in the future.

The findings of increased negative self-schemas in patients with a first-episode of psychosis could also be used to influence treatment priorities. Techniques such as compassion focused therapy (CFT; Gilbert, 2010) focuses on the development and enhancement of compassion for the self and others and may go some way to reduce negative schemas and/or enhance the positive schemas of individuals with psychosis. Studies of CFT in individuals who hear malevolent voices have shown some promise with reductions found in malevolence, persecution and increased self-reassurance, as well as decreases in symptoms of depression, psychoticism, paranoia, anxiety, OCD, and interpersonal sensitivity (Mayhew & Gilbert, 2008). As yet, no studies have looked into treating negative beliefs in particular, but a proxy for this process (low self-esteem) has been used as target for treatment, with some encouraging findings (Lecomte et al., 1999; Hall & Tarrier, 2003). However, it has previously been argued that these processes are not entirely comparable (Fowler et al., 2006b), and clearly more research is needed that focuses on treating negative self-beliefs in particular.

8.5. Future directions

Further research possibilities within the existing CAPsy study

There are several ways in which future research can extend the findings of this thesis using data from the existing CAPsy study; potentially by introducing new variables into the analysis and utilising data which was not available in time for this thesis. However, it is important to note that the following suggestions are by no means exhaustive, and there are a whole host of possible future directions. In terms of introducing new variables into the analysis, there is more research to be done with regard to exploring the impact of other demographic factors on the relationship between life events and psychosis, in particular, ethnicity. Although some researchers have suggested that people of African and Caribbean background may be more likely to experience an acute psychotic disorder in response to adverse life events (Littlewood & Lipsedge, 1982), previous empirical studies have not found an increased rate of negative life events in black and minority ethnic (BME) groups, compared with the white British population (Hutchinson et al., 1998; Gilvarry et al., 1999). However, due to the high proportion of BME participants in this sample, it would be an important avenue for future research. Possible analyses could include testing for the presence of an interaction between ethnicity, life events and psychosis.

Another consideration for future research that would incorporate existing data within the CAPsy study is to consider the impact of social adversities on the individual symptoms of psychosis, rather than looking at the disorder as a whole. Psychosis is a heterogeneous phenomenon covering a wide range of psychiatric diagnoses, and therefore its symptoms are unlikely to be the product of a single causal process. Different adversities are unlikely to act on the same cognitive and emotional processes, and influence the same symptoms. Focusing on individual symptoms is a common approach adopted by psychologists when researching and treating mental health problems and has recently been strongly advocated by the US National Institute of Mental Health through their Research Domain Criteria strategy (Sanislow et al., 2015). A specific symptom approach has recently been adopted by researchers investigating the association between childhood adversity and psychosis, to see whether there are differential mechanistic pathways to psychosis following exposure to different types of adverse experiences (Bentall et al., 2014). Therefore, it would also be useful to investigate whether there are differential effects of specific events in adulthood on individual psychotic symptoms and elucidate the mechanisms that may underlie these associations (Beards & Fisher, 2014). Data was not yet available to assess differential effects of recent stress exposure on individual symptoms, including paranoid delusions and auditory hallucinations, but research indicates that there may well be differences across symptoms (Bentall et al., 2014). Intrusive events have been hypothesised to be ‘paranoia-inducing’ (Harris, 1987), and therefore we may expect these to be most associated with experiences of paranoid delusions.

It should also be noted that although this thesis has focused solely on specific social and psychological mechanisms, it does not disregard the role of genetic and biological factors, as well as other social and psychological factors in the aetiology of psychosis. Other factors such as gene x environment interactions (Stefanis et al., 2007), cortisol (Walker & Diforio, 1997), structural brain changes (Papagni et al., 2011), have also shown associations with life events and psychosis, and it is therefore important that the findings of this thesis are viewed within a broader biopsychosocial model. The mechanisms involved in the aetiology of psychosis are not mutually exclusive and may be linked to one another via a causal chain, or interact to increase the risk of disorder. Thus, in order to progress this work and deliver valuable therapeutic advances, collaborations will be required across multiple disciplines. Since the CAPsy study collected a vast array of information, including on genes, cortisol and brain structure, numerous collaborations are possible for future publications and extension of this thesis.

New research ideas to advance understanding of the life events-psychosis association

As well as considering possibilities within the existing dataset, it is also important to think about new research ideas to advance the understanding of the life events-psychosis association, and how best to go about this in a new and original study. If utilising a similar case-control design, one possibility could be to make the focus of the study on further exploring the impact of social risk factors in adulthood, rather than collecting information on multiple risk factors across the lifetime. This refined focus could allow for more resources to recruit an even larger sample, and potentially include a corroboration element by recruiting close family members to verify aspects of the life events interview. A larger case-control sample would increase the power when considering the impact of specific life event characteristics, and corroboration could increase reliability and minimise the impact of recall bias.

However, in order to advance this field even further, the ideal would be to move on from identifying specific environmental and social risk factors, to an examination of the influence of multiple exposures, how they interact with each other, and the mechanisms underlying their relationships to psychosis (Hatch, 2005). However, in order to perform these sophisticated investigations and analyses, there is clearly a need for large population samples where the focus can only be on subclinical symptoms if the sufficient numbers needed for these analyses are to be gained. Given the potentially low power for many of the analyses in this thesis, and particularly for the synergistic and mediational effects of schemas and affective symptoms, it would be interesting to further explore these ideas in samples of a sufficient size, focusing on PLE within the general population.

In order to get a better handle on temporal associations, it would also be interesting to consider associations between life events and psychosis using a longitudinal design. As mentioned above, future research should try to make use of large general population samples, either via existing cohorts such as the Environmental Risk Longitudinal Twin Study (E-Risk) (Moffitt, 2002), or to consider setting up a new cohort study from scratch. A possible idea would be to move into the area of youth mental health as it is clear that in order to improve the mental health of future generations, there must be a focus on improving youth mental health outcomes (McGorry et al., 2007). This is especially the case for individuals living in major cities, where exposure to severe and intrusive experiences are undoubtedly higher, and the rates of psychosis are greater than for a non-urban environment (Krabbendam & van Os, 2005). As more of the world's population moves to cities, with rates increasing from

roughly 40% in the mid-1970s, to a predicted 60% by 2025 (World Bank, 2000), it is clear that the need to address the challenges of inner-city life are becoming more urgent. Research that focuses on exploring the factors which interact with stress to increase the risk of subclinical psychotic experiences within adolescent samples, may lead to an increased understanding of the journey to psychosis and uncover new targets for early intervention.

In terms of specifically advancing the work that has been presented in this thesis, it would be interesting to further explore the impact of negative core beliefs on the development of PLE. Theory suggests that negative core beliefs are developed early in life, potentially after exposure to adverse experiences (Garety et al., 2001; 2007), and therefore it would be interesting to test the impact of these beliefs on the association between adverse events and psychosis, at a point in time much closer to their theorised conception. This could significantly reduce the impact of recall bias and allow for relationships of cause and effect to be more confidently identified. If the sample size and resources allow, individuals could potentially be followed up into adulthood to see whether exposure to adverse events predict the persistence and/or severity of PLE, and a possible transition to psychotic disorder. Furthermore, if evidence for an interaction is found in a much younger population, then treatments which target the minimisation or control of negative beliefs, such as cognitive bias modification and mindfulness, could also be trialled in an adolescent sample.

Another idea for new research is to consider different methodologies, particularly making use of technological advances. Although the gold-standard for assessing life stress is the LEDS (Brown & Harris, 1989a), this measure is now over three decades old, and a consideration of new methodological possibilities is needed in order to advance the field of stress research. One possibility which is in the early stages of exploration by Antonia Bifulco's group at Kingston University, is a computerised LEDS interview, completed by the participant using a tablet device and scored using a computer-generated algorithm. Computerised measures which make use of algorithmic scoring have been shown to be a successful addition to modern psychiatric research, e.g. for generating research diagnoses in adults (OPCRIT; McGuffin et al., 1991), but these methods have not yet been applied to the assessment of complex social risk factors. This innovative method has enormous potential as it will be able to generate rich data, comparable to a conventional LEDS interview, but will be more cost-effective and have wider research and health practice utility. It shows great promise to advance aetiological

understanding of the association between life events and psychosis, and a host of other physical and psychiatric conditions.

8.6. Final conclusions

This thesis has identified a specific association between severe and intrusive life events and difficulties and the onset of psychosis that is reasonably robust to the potentially confounding effects of demographic factors, cannabis use and indirect genetic risk for psychosis. Possible psychological mechanisms through which recent threatening experiences may impact on the later development of psychotic disorder have been explored, and there is some tentative evidence that low social class and negative self-schemas combine with severe experiences in adulthood to increase the odds of psychosis. These factors represent possible avenues for intervention and treatment, but replication of these findings is required in larger samples using a robust epidemiological design and comprehensive measures of both recent stressful experiences and psychosis. A wider range of potential biological, psychological and social mechanisms should also be considered. Overall, this thesis has shown that the one year period before the initial onset of psychosis is a time of serious psychosocial stress for most patients and understanding the complex interactions between these stressors and their potential links to psychosis is likely to provide guidance concerning therapeutic and preventative targets.

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APPENDICES

APPENDIX A - Quality Assessment for Life Events and Psychosis Research

Selection Bias

Are the individuals selected to participate in the study likely to be representative of the target population?

Score

- | | |
|---|---|
| 0 | There was a non-random selection process or the sampling method was not reported. |
| 1 | The sample was made up of either incident cases <u>or</u> randomly sampled controls, or there were no control subjects. |
| 2 | In case-control/cohort studies, the sample was made up of incident cases and randomly sampled controls. In general population studies, the entire sample was randomly selected. |

What percentage of selected individuals agreed to participate?

Score

- | | |
|---|---|
| 0 | Less than 50% of participants, or not reported or not applicable. |
| 1 | 50-69% of participants. |
| 2 | 70-100% of participants. |

What is the sample size?

Score

- | | |
|---|--|
| 0 | Less than 50 subjects in each group |
| 1 | At least 50 subjects in each group |
| 2 | At least 100 cases and controls or sample size calculation indicating adequate statistical power |

Measurement of Life Events

What was the quality of the life events measurement tool?

Score

- | | |
|---|------------------------------------|
| 0 | Self-report checklist |
| 1 | Interviewer administered checklist |

2 Semi-structured interview

Was event independence taken into consideration?

Score

- | | |
|---|---|
| 0 | No distinction was made between different life events, or not reported. |
| 1 | There was an assessment of event independence but these events were not treated separately in the analysis. |
| 2 | There was an assessment of independent versus possibly dependent life events and these events were analysed separately. |

Measurement of Psychosis

How was psychosis measured?

Score

- | | |
|---|---|
| 0 | Clinician-only diagnosis |
| 1 | Structured assessment by trained research worker, or self-report measure for psychotic-like experiences |
| 2 | Structured assessment by clinician |

Confounding

Was there an assessment of confounding in the analysis?

Score

- | | |
|---|--|
| 0 | No adjustment for confounders |
| 1 | Adjustment for basic demographics e.g. age, gender, ethnicity, socioeconomic status |
| 2 | Potential confounders were measured and adjusted for in the analysis e.g. adjustment of basic demographics and other risk factors such as urbanicity, drug/alcohol use, social support |

N.B. scores of 10 or more (70% or over) were considered to indicate methodological quality.

APPENDIX B - Supplementary Information for the Meta-Analysis

Methods

Data extraction

The data was extracted from each study including the outcome and possible moderator variables: year of publication, life events period, population (whether clinical or general population) and methodological quality score (score out of 14). Where frequencies were reported, the log odds ratio and its standard error were calculated; where odds ratios and confidence interval were reported, these were transformed onto the log scale and the standard error calculated; where mean number of events was reported, this was assumed to be the mean from a Poisson process and the number experiencing one or more events was estimated. Where outcome had been reported for a variety of values, for instance life event period, the choice was governed by the desire to have this as consistent as possible across studies.

Data analysis

A standard random effects meta-analysis using inverse variance weighting was carried out with metafor (Viechtbauer, 2010) using REML. Heterogeneity is reported using Higgins' I^2 with 95% confidence intervals. Further exploration of heterogeneity was carried out using meta-regression using the available possible moderator variables: year of publication, life events period, quality score, (all three as scores) or population studied (a two-level factor: clinical versus general population). The results are displayed using a forest plot (see Figure 1). Model fit was further examined using leave-one-out diagnostics (Viechtbauer & Cheung, 2010). Small study bias was examined visually using funnels plots and tested with the usual regression tests.

Results

The meta-analysis of thirteen studies yielded an overall weighted odds ratio of 3.19 (95% CI 2.15-4.75). Figure 1 shows the forest plot from the analysis without moderators. There was substantial heterogeneity between studies (Higgins' $I^2=87.27\%$ (95% CI 70.34%-96.36%). This heterogeneity was not removed by meta-regression using any of the four possible moderators possibly due to rather restricted variability on all of them. There is no obvious sign of asymmetry in the funnel plot (not shown) which is also confirmed by the usual rank and regression tests. Examination of the fit of the model using leave-one-out diagnostics (Viechtbauer & Cheung, 2010) did not reveal any unusual features apart from the outlier obvious in Figure 1 (Gureje).

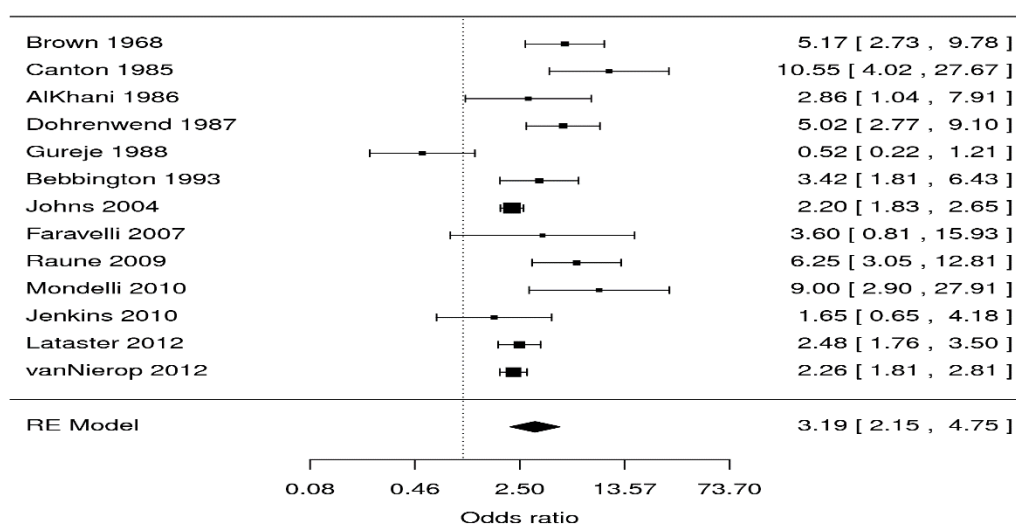


Fig. 1. Forest plot for the meta-analysis examining the overall association between recent life events and psychosis.

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APPENDIX C - Patient Information Sheet and Consent Form

Information and Consent Form (not for data entry)

You have been asked to take part in a study being conducted in the South London and Maudsley NHS Trust. Before you decide whether to enter the study, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information and ask any questions if something is not clear or you wish to know more.

TITLE OF PROJECT: GENETICS AND PSYCHIATRIC ILLNESS (GAP)

What are the aims of the study?

In our research project we are interested in identifying what the main risk factors that predispose to psychosis are. In particular, we want to know whether there are any genes that increase the risk of developing a psychotic disorder, either alone or by interacting with environmental factors such as stress, cannabis, and infections. Part of the reason why some people become ill may lay in genetic differences between people, in the same way that we are different in the colour of our eyes, hair etc. To achieve this, we will compare the genetic make-up of people with a diagnosis of psychosis with the make-up of people with similar characteristics but no history of mental health problems.

We also aim to establish whether some genes might influence the course of the illness and response to medication. Some patients experience an improvement of their psychiatric symptoms when they are treated with medications, whereas others do not do so well and/or experience severe side-effects. Therefore we aim to look at how genes can influence individual differences in response to drug treatment so that we may be able to choose better drugs for each person. The type of genetic analysis that we carry out is only for research purposes and does not at present produce clinically relevant results.

Finally, an additional aim of the study is to understand how the social environment may contribute to the onset of illness and the illness experience.

Why are we asking for your help?

You have been invited to take part in this study because of the nature of the symptoms that you appear to have been experiencing. During the course of the study approximately 1000 people who have had symptoms like yours will be asked to take part.

Note that a patient does not have to be involved in the GAP project research and, if they decide not to take part, it will not affect their current or future medical care in any way.

What will we ask of you if you take part in the study?

For this project we will ask from you a small sample of blood, about 20 mL (a few tablespoons full) or cheek swab and saliva samples for metabolic and genetic analysis. We may also use your blood and saliva sample to:

Measure the level of hormones and proteins contained in the blood serum and in the saliva.

Look at the expression of some genes of interest in the white cells contained in the blood.

A medically trained researcher will take the blood sample using disposable sterile equipment. It will only take few minutes as for any routine blood sample. If you are unable or unwilling to give a blood sample it is also possible to perform genetic analysis from cheek swab samples, a simple procedure that (we can show you the kit and illustrate the procedure) collects dead cells present in your saliva and in your mouth. From the cheek swab sample we cannot measure level of medication or look at expression of genes, we can only extract a small amount of DNA. Therefore we prefer to ask for a blood sample to guarantee a better quality of our results and make the most out of your generous help.

A researcher will demonstrate how to collect the saliva sample and will provide you with the tubes required. The level of some proteins contained in the saliva can give us an indication of differences in the level of stress experienced by healthy volunteers and people suffering from mental illnesses.

We will also ask for some of your time to collect clinical and socio-demographic information using standardised research instruments: diagnostic interview, symptoms rating scale, socio-demographic interview and neuropsychological tests. We may also ask you to participate in an interview asking about your own perspectives on your social environment and your health condition.

If you have already taken part in other research projects at the Institute of Psychiatry, London that involved some of the assessment we are interested in, we will not ask you to undergo them again but we request your permission to use the existing data.

Some people within the study will be invited to undergo an MRI scan of the head and of another region of the body (the adrenal gland, a small gland above the kidney). They will be presented with separate information and consent forms for this procedure.

The sample collection and the clinical assessment will require approximately 3 hours of your time. Moreover we would like to contact you again for follow up (up to 24 months) to repeat the above assessments to investigate changes over time. We will also reimburse any travel expense related to your participation into the study.

We will also ask for your consent to contact your GP, mother (or father) and a sibling. This is 1) to collect information from your GP records and mother about events that may have occurred very early in your life, such as complications during pregnancy and neonatal infections, 2) to conduct some of the same assessments with your sibling that we have conducted with you, and

3) to ask your sibling similar questions that we have asked you about the environment in which you both grew up and experiences you may have had in childhood. We will only contact your GP and/or relative(s) with your explicit consent and we will not disclose any information we have collected from you to them. If you agree for us to contact your mother (or father) and/or a sibling, we will only proceed to interview them if they provide consent.

What are the risks?

The risks involved are those of ordinary blood tests such as small pain and occasionally a small bruise around the area from where the sample has been taken. There is no risk involved in the collection of saliva.

Is Confidentiality guaranteed?

All personal information about you is regarded as strictly confidential; only researchers belonging to the study team, and not external collaborators, know which sample belongs to whom. All the information about you will be coded; you will not be identifiable in any research outcome.

The blood samples first and the DNA samples after extraction will be stored in the Institute of Psychiatry secured laboratory until reporting is complete.

The samples will be coded using bar codes (numbers and letters not referring to your name or date of birth) that will be entered on a secure computerized data base.

The clinical information collected on the sample will be securely held in the Institute of Psychiatry building.

Nothing that you have told us will be mentioned to any relative you might give us permission to contact.

The access to the samples and the related information will be restricted to the researchers involved in the study. In case of commercial collaborations only the coded data will be shared, therefore no researcher external to the study team will ever have access to personal data concerning participants.

Any future work will pursue aims related to the topic of this project and any extension of the project beyond 5 years, will be subject to review by a research ethics committee. You are free to withdraw from this study at any point without giving a reason by contacting the researcher whose details are at bottom of the consent form. Withdrawal will not affect any of the care and treatment you receive.

What are the benefits for you of taking part?

This is a research project, looking at comparing a group of healthy volunteers with people experiencing their first psychotic episode. As mentioned before, this study will not produce individual test results for any of the data collected. Therefore we cannot offer direct benefits for you. We will be able to provide all participants with a general summary of our research, when

the project is complete, through a project newsletter. Our research study is also described on the Institute of Psychiatry general website (www.iop.kcl.ac.uk), under the Department of Psychosis Studies section.

Who is funding this project?

This study is funded by the The Maudsley Charitable Fund, the Department of Health, **the Wellcome Trust and the European Union**. Thank you very much for your time and once again please ask for more information on both the project and/or your illness/symptoms if it is still unclear.

Contact details for research team:

Dr Marta Di Forti
Institute of Psychiatry
Tel 020 7848 5352
e-mail: marta.diforti@kcl.ac.uk

CONSENT FORM

If you have come to the decision to enter the study after carefully considering the information provided, please read and sign this form.

TITLE OF PROJECT: GENETICS AND PSYCHIATRIC ILLNESS (GAP)

Researcher: Dr Marta Di Forti, Institute of Psychiatry

I have read the information sheet and I have been given a copy. I was given the opportunity to ask questions. I understand why the research is being done and the risks involved.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
I agree to give a sample of blood/cheek swab and saliva samples for research in the above project. I understand how the sample will be collected, that giving the sample is voluntary and that I am free to withdraw at any time without giving a reason, and without my medical treatment or legal rights being affected. I understand that I will be contacted in the future to repeat part of the assessment.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
I understand that research using the sample I give will involve genetic analysis aimed at understanding the role of genes in disease and response to drugs, that the data produced are for research rather than clinical purposes, and that these results will have no implications for me personally.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
I understand I will not receive any 'test' results from this study , because the assessment I will undergo, does not produce clinically relevant information but just research data. The project newsletter will describe the general importance of any research results obtained.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
I give permission for my previous research records to be looked at, and information from them to be analysed in strict confidence by responsible professional staff from the research team. Researchers external to the study team, collaborating in the project (including commercial collaborations) will only access my coded data.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
I agree that the samples I have given and the information gathered about me can be examined and stored until reporting is complete at the Institute of Psychiatry. I understand that future authorised research may be performed by researchers other than those who conducted the first project, including researchers from commercial organisations. To guarantee confidentiality, I agree that researchers external to the study team, including those from commercial collaborators, will only have access to coded data and not to personal details. Any future research will only pursue aims related to the topic of this project, and any extension of the project will be subjected to review by a research ethics committee.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

<p>I consent to the input of coded data obtained from my blood sample and from the information gathered about me into a computer, to be used for statistical analysis and research. I understand I have the right to request, via the study co-ordinator, to review data concerning me, and to have such data modified if inaccurate, or deleted.</p>	<p>Yes <input type="checkbox"/></p>	<p>No <input type="checkbox"/></p>
--	--	---

<p>I consent to participate in a digitally-recorded interview about my own perspectives on my health condition and on my social experiences. I understand that this interview would be recorded to ensure that my own views are adequately represented.</p>	<p>Yes <input type="checkbox"/></p>	<p>No <input type="checkbox"/></p>
--	--	---

<p>I understand I will not benefit financially if this research leads to the development of a new treatment of medical test but my travel expenses will be reimbursed.</p>	<p>Yes <input type="checkbox"/></p>	<p>No <input type="checkbox"/></p>
---	--	---

<p>I give permission for my GP records to be looked at.</p>	<p>Yes <input type="checkbox"/></p>	<p>No <input type="checkbox"/></p>
--	--	---

<p>I agree to my mother being approached to participate in this study.</p>	<p>Yes <input type="checkbox"/></p>	<p>No <input type="checkbox"/></p>
---	--	---

Contact details:

Name

Address

.....

Phone Number

<p>I agree to a sibling being approached to participate in this study.</p>	<p>Yes <input type="checkbox"/></p>	<p>No <input type="checkbox"/></p>
---	--	---

Contact details:

Name

Address

.....

Phone Number

.....
Name of Subject	Date	Signature

.....
Name of Researcher	Date	Signature

	Yes	No
<i>Would you like to be sent further information about the project in our newsletter?</i>	<input type="checkbox"/>	<input type="checkbox"/>

Contact details for research team:

Dr Marta Di Forti
Institute of Psychiatry
Tel 020 7848 5352
e-mail: marta.diforti@kcl.ac.uk

APPENDIX D - Psychosis Screening Questionnaire (PSQ)

Subject number: 2EU02. |__|_|_|_| Date of Birth |__|-|__|-|1|9|_|_|

Time interval: Lifetime

Interviewer: **Date** |_|_|-|_|_|-**2**|**0**|_|_|

Code: No = 0 Unsure = 1 Yes = 2

In this survey we have to ask about a whole range of experiences. Some of these experiences are quite rare. However, I would be very much obliged if you would bear with us and answer the questions I am going to ask you now.

Q1. Over the past year, have there been times when you felt very happy indeed without a break for days on end?

(a) Was there an obvious reason for this?

(b) Did your relatives or friends think it was strange or complain about it?

Q2. Over the past year, have you ever felt that your thoughts were directly interfered with or controlled by some outside force or person?

(a) Did this come about in a way that many people would find hard to believe, for instance through telepathy?

Q3. Over the past year, have there been times when you felt that

people were against you?

(a) Have there been times when you felt that people were deliberately acting to harm you or your interests?

☐

(b) Have there been times when you felt that a group of people was plotting to cause you serious harm or injury?

☐

Q4. Over the past year have there been times when you felt that something strange was going on?

☐

(a) Did you feel it was so strange that people would find it very hard to believe?

☐

Q5. Over the past year, have there been times when you heard or saw things that other people couldn't

☐

(a) Did you at any time hear voices saying quite a few words or sentences when there was no-one around that might account for it?

☐

Q6. Have you ever received treatment for any psychiatric or psychological problem?

.....

APPENDIX E - Life Events and Difficulties Schedule

Interview

Time Period _____ (12 months pre-onset) to _____ date of onset

[INTERVIEW]

Doubt

At the end of the interview, rate the degree of confidence/doubt in the accuracy of subject's recall/self-report. This is the interviewer's subjective impression, and is designed to indicate the existence of any reasons for doubting the accuracy of the subject's responses. In addition, include doubt about accuracy of information due to failure to fully probe by interviewer. Describe as fully as possible any reasons for doubt.

- 0. No doubts
- 1. Doubt – Recall possibly influenced by symptoms, mental state
- 2. Doubt – Interviewer failed to clarify
- 3. Doubt – Other

☐

Describe reasons for doubt below

Interview

Each section refers to a particular group of life events or difficulties category but in the course of the interview a question may throw up information about another life event or difficulty and this should also be probed for carefully. Each section begins with obligatory opening questions (in bold) followed by probes that should only be used where a positive response has followed from the opening question. A brief description of any event or difficulty should be recorded.

Notes

1. All questions relate to the 12-month period before onset. Date of onset should be established, as far as possible, prior to the interview. The 12-month time period being considered should be referred to throughout. The phrasing of questions must reflect this, for example: have you been ill in the past 12 months (for cases with very recent onset); were you ill at any time during that period [specify period, e.g.

May 2007 to May 2008].

2. For all difficulties, establish when they started and whether the level has changed.

3. FOR EVERY EVENT OR DIFFICULTY REMEMBER: Always establish the dates.

4. FOR EVERY EVENT OR DIFFICULTY REMEMBER: Probe for when problem was solved.

Introduction

Now, I would like to ask about the 12 month period before ... [onset, from NOS]. I would like to ask questions about things that may have happened to you, or to people close to you during that 12 month period. The questions I ask will relate to your partner, children, siblings, parents, other members of household, and very close friends. Before I ask about things that may have happened, can I begin by asking ...

Friends, Confidants

- Is there anyone, either family or friends, that you feel very close to? Anyone else?
(Note main confidants)
- If you had a problem of some sort, who would be the first person you would want to discuss it with?
- Who else can you confide in about personal things or worries?
- Are your answers the same for the 12 month period prior to onset, or have things changed since then?

Support

For each event or difficulty of probable moderate or marked threat, probe for support (if any) received ...

Did you tell anyone about it?

If **yes** **When did you first tell someone?**

Were they helpful?

Were they sympathetic?

Was anyone particularly helpful? Who?

What did they do or say?

I would like begin by asking you some questions about health (all of which relate to the 12 months before onset) ...

1) HEALTH, ACCIDENTS, DEATHS

Have you or anyone else been ill?

If **yes** How serious was it? An emergency? Has anyone been off work because of it?

Have you or anyone else been admitted to or left hospital?

If **yes** For what sort of illness or injury?

If it is a long term problem, **ASK**: is the problem still ongoing? (i.e., to point of onset for cases)

Have there been any other health problems at all that you might have overlooked?

[For example, have there been any surgical operations in the last 12 months? Have you had any bad news about an illness that has been going on for some time? Are there any long term health problems affecting anyone close?]

Have you or anyone else had an accident? (either a car accident, as a pedestrian, or at home)

If **yes** What happened? How serious was it?

Has anyone close to you died? (Prompt for family, members of household, close friends)

If **yes** Was it unexpected? Were you involved at all? Were you present?

Has anyone attempted suicide?

Has anyone else died or nearly died?

Can I now ask you some questions about relationships?

2) RELATIONSHIPS, INTERACTION CHANGES

If in a long-term relationship (6 months or more) or living with partner ...

How well would you say that you and your partner get on in general?

Would you say there are any problems in your relationship?

How often do you and he/she argue or have rows? Have there been any other problems to do with money, work, relatives such as in laws or any sexual problems?

Have either of you ever considered a separation or divorce?

Have you been separated for any length of time?

If **yes** For how long were you apart?

For all ...

Have any relationships ended?

If **yes** Why did that happen when it did?

Have you lost contact with anyone who used to be close?

Is there anyone (else) whom you see much less of than you used to?

Have you had any other crises in the family or involving close friends? (e.g., major argument)

For all interaction change events, **probe**: Temporary? How long away? How often seen before the change? How much did you do together? How often do you see each other now? Distance, Telephone contact; How did you get along? How about now? Preparation? Evidence of rejection, guilt

3) BIRTHS, CHILDREN

Have you or anyone in the family or any close friends been expecting a baby or had a baby?

If **yes** Was it planned? Did the birth go smoothly?

Have your children had any problems at school (e.g., truancy) or have they been a problem at home?

Do you worry about their friends?

Any other problems with your children?

I'd now like to move on to ask about work and/or studies ...

4) WORK, EDUCATION

If subject currently working ...

Do you enjoy your job?

Has anything notable happened at work?

Have you been off work at all or put into a new job or changed jobs?

How do you get on with your work colleagues? Have you had any trouble or difficulties with them?

Have you been out of work at all?

If **yes** How long were you out of work? Were you looking for a job or did you prefer to stay at home? How did your previous job come to an end?

If subject not currently working ...

How did your last job come to an end? (Probe: redundancy, sacked, left for other reason)

If subject currently studying (or been studying in 12-month period) ...

Have you any problems at school or college? (Probe: with course work, fellow students, teachers)

5) FINANCES, HOUSING

Have you had any money worries during ...?

If **yes** Have you gone without things you really need? Have you had problems paying bills, the rent or mortgage? Have you had any debt problems? Have you tried to borrow from anybody?

Have you had any problems with your housing or neighbours?

Have you had any changes regarding housing or neighbours?

Any other housing problems?

Possible **probes**: Why did you move? What happened? Decision to move? Were there any difficulties? Have there been any difficulties since? Expense; Consequences; Did you feel cut off? (friends, babysitters, etc.); New friends; Impact on jobs; Any problem re: house/neighbours, etc.

6) CRISES, VICTIMISATION, LEGAL

Has there been any crises or emergencies of any kind?

Has anything valuable been stolen or lost or has your home been broken into in the last six months?

Has anyone been attacked or assaulted?

Have you witnessed an assault or other traumatic event?

Have you or anyone in your family had any contact with the police or lawyers or court, at all?

If **yes** Nature of offence; First time done it; First time in court; Other convictions; Verdict and sentence; Financial implications; What have other people said; What have they said at work; Driving affected (if licence lost, etc.); Implications re: other people involved; Were you afraid they would try to get their own back?

Sometimes people find they undergo difficulties connected with living in the UK, such as problems with visas, immigration authorities, or perhaps discrimination against you by others.

Have you experienced anything like this in this period?

A couple of final questions ...

Sometimes people learn unexpected things about others close to them such as discovering their friend has been stealing, or their partner has been seeing someone else. **Has anything like this happened to you?** (e.g., something that changes your idea of the person's character?)

Anything else like that?

Any other event (positive or negative) that we've not discussed? Any other ongoing problems or difficulties?

EVENTS AND DIFFICULTIES

Ratings

Rate all events on score sheet, if possible in order of occurrence, using the LEDS rating scales below.

RATINGS**Focus****1 Subject focussed**

(1) Subject focussed

(2) Joint focussed with other(s)

2 Other focussed

(3) Focussed on a possession or pet

(4) Focussed on another person(s)

Independence(Extent to which the occurrence of the event is likely to be independent of any hypothetical presence of disorder.)**1 Independent****2 Possibly Dependent****Threat (Severity)**

(The degree of unpleasantness i.e. ongoing negative feelings associated with the event/difficulty, and threat i.e. uncertainty and anticipation of difficult consequences associated with the event)

Events**1 Marked threat, unpleasantness****2 Moderate threat, unpleasantness****3 Some threat, unpleasantness****4 Little, none****Difficulties****1. High marked****2. Low marked****3. High moderate****4. Low moderate****5. Mild****6. Very mild****7. Not/no longer a difficulty****Intrusiveness****1 Marked intrusiveness****2 Moderate intrusiveness****3 Some intrusiveness****4 Little or no intrusiveness****Overall Support****0 High**Satisfactory emotional **and** practical support received. Subject able to confide, felt supported by one (or more) person who helped participant deal with the event (or difficulty)**1 Moderate**Satisfactory emotional **or** practical support from one (or more) person but may not have been enough to help participant deal with what event (or difficulty)**2 Some**

Brief or minimal support was received that was limited in its helpfulness

3 None

No support received

Negative Support**3 High**

Clear statement that participant is to blame or deserved what happened

2 Moderate

Participant is accused of lying about event (or difficulty) or insinuation that was to blame

1 Some

Confiding ignored or some disbelief expressed

0 None

Positive or neutral response

EVENTS AND DIFFICULTIES

Score sheet

Complete ratings for event. Write a brief description of each event on the reverse.

*	†	(1) Focus	(2) Start date	(3) End date	(4) Duration (months)	(5) Independence	(6) Threat (Severity) ‡		(7) Intrusiveness	(8) Support#	
							s - t	l- t		+	-
		<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
		<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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		<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

* Number events and difficulties, signifying 'e' for event and 'd' for difficulty, i.e. e1, e2, e3 etc. and d1, d2, d3, etc.

† Specify event or difficulty type

‡ For events rate s-t and l-t; For difficulties rate l-t only

s-t short-term threat

l-t long-term threat

+ Overall

- Negative

Descriptions (continue over page or on separate sheet, if necessary)

APPENDIX F - Brief Core Schema Scales

ID number: _____

Date of completion: _____

Rater Initials: _____

This questionnaire lists beliefs that people can hold about themselves and other people. Please indicate whether you hold each belief (NO or YES). If you hold the belief then please indicate how strongly you hold it by circling a number (1–4). Try to judge the beliefs on how you have generally, over time, viewed yourself and others. Do not spend too long on each belief. There are no right or wrong answers and the first response to each belief is often the most accurate.

1 Believe it slightly

2 Believe it moderately

3 Believe it very much

4 Believe it totally

MYSELF

I am unloved	NO	YES	→	1	2	3	4
I am worthless	NO	YES	→	1	2	3	4
I am weak	NO	YES	→	1	2	3	4
I am vulnerable	NO	YES	→	1	2	3	4
I am bad	NO	YES	→	1	2	3	4
I am a failure	NO	YES	→	1	2	3	4
I am respected	NO	YES	→	1	2	3	4
I am valuable	NO	YES	→	1	2	3	4
I am talented	NO	YES	→	1	2	3	4
I am successful	NO	YES	→	1	2	3	4
I am good	NO	YES	→	1	2	3	4
I am interesting	NO	YES	→	1	2	3	4

OTHER PEOPLE

Other people are hostile	NO	YES	→	1	2	3	4
Other people are harsh	NO	YES	→	1	2	3	4
Other people are unforgiving	NO	YES	→	1	2	3	4
Other people are bad	NO	YES	→	1	2	3	4
Other people are devious	NO	YES	→	1	2	3	4
Other people are nasty	NO	YES	→	1	2	3	4
Other people are fair	NO	YES	→	1	2	3	4
Other people are good	NO	YES	→	1	2	3	4
Other people are trustworthy	NO	YES	→	1	2	3	4
Other people are accepting	NO	YES	→	1	2	3	4
Other people are supportive	NO	YES	→	1	2	3	4
Other people are truthful	NO	YES	→	1	2	3	4

APPENDIX G - Hamilton Depression Scale

Structured interview guide for the Hamilton-Depression Rating Scale (SIGH-D)

Interviewer: The first question for each item should be asked exactly as written. Often this question will elicit enough information about the severity and frequency of a symptom for you to rate the item with confidence. Follow-up questions are provided, however, for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain necessary information.

Notes:

Time period: Although the interview questions indicate that the ratings should be based on the patient's condition in the past week, some investigators using this instrument as a change measure may wish to base their ratings on the previous two to three days. If so, the questions may be preceded by "In the last couple of days..."

Loss of weight item: It is recommended that this item be rated positively whenever the patient has lost weight relative to their baseline weight (i.e. before their current episode of depression), provided that they have not begun to gain back lost weight. Once the patient has begun to gain weight, however, even if they are still below their baseline, they should no longer be rated positively on this item.

Referent of 'usual' or 'normal' condition: Several of the interview questions refer to the patient's usual or normal functioning. In some cases, such as when the patient has Dysthymia or Seasonal Affective Disorder, the referent should be to the last time they felt OK (i.e. not depressed or high) for at least two weeks.

Overview: I'd like to ask you some questions about the past week.

How have you been feeling since last (DAY OF WEEK)?

IF OUTPATIENT: Have you been working? IF NOT: Why not?

1. Depressed Mood (sadness, hopeless, helpless, worthless)

SCORE_____

What's your mood been like this past week?

Have you been feeling down or depressed?

Sad? Hopeless?

In the last week, how often have you felt (OWN EQUIVALENT)? Every day? All day?

Have you been crying at all?

0 – absent

1 – indicated only on questioning

2 – spontaneously reported verbally

3 – communicated non-verbally, i.e. facial expression, posture, voice, tendency to weep

4 – VIRTUALLY ONLY; this in spontaneous verbal and non-verbal communication.

N.B. IF SCORED 1-4 ABOVE, ASK: How long have you been feeling this way?

2. Work and Activities

SCORE_____

How have you been spending your time this past week (when not at work)?

Have you felt interested in doing (THOSE THINGS) or do you feel you have to push yourself to do them?

Have you stopped doing anything you used to do? IF YES: Why?

Is there anything you look forward to?

(AT FOLLOW-UP: has your interest been back to normal?)

0 – no difficulty

1 – thoughts and feelings of incapacity, fatigue, or weakness related to activities, work or hobbies.

2 – loss of interest in activity, hobbies or work – by direct report of the patient or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities).

3 – decrease in actual time spent in activities or decrease in productivity. In hospital, patient spends less than 3 hours/day in activities (hospital job or hobbies) exclusive of ward chores

4 – stopped working because of present illness. In hospital, no activities except ward chores, or fails to perform ward chores unassisted.

3. Genital Symptoms (e.g. loss of libido, menstrual disturbances) SCORE_____

How has your interest in sex been this week? (I'm not asking about performance, but your interest in sex – how much you think about it.)

Has there been any change in your interest in sex (from when you were not depressed)?

Is it something you've thought much about? IF NO: Is that unusual for you?

0 – absent

1 – mild

2 – severe

4. Somatic Symptoms - Gastrointestinal SCORE_____

How has your appetite been this past week? (What about compared to your usual appetite?)

Have you had to force yourself to eat?

Have other people had to urge you to eat?

0 – none

1 – loss of appetite but eating without encouragement

2 – difficulty eating without urging

5. Loss of Weight (Rate either A or B): SCORE_____

Have you lost any weight since this (DEPRESSION) began?

IF YES: How much?

IF NOT SURE: Do you think your clothes are any looser on you?

AT FOLLOW-UP: Have you gained any of your weight back?

A – When rating by history:

0 – no weight loss

1 – probable weight loss associated with present illness

- 2 – definite (according to patient) weight loss
- 3 – not assessed

B – On weekly ratings by ward staff, when actual weight changes are measured:

- 0 – less than 1 lb. loss in week
- 1 – more than 1 lb. loss in week
- 2 – more than 2 lb. loss in week
- 3 – not assessed

6. Insomnia Early

SCORE_____

How have you been sleeping over the last week?

Have you had any trouble falling asleep at the beginning of the night? (Right after you go to bed, how long is it taking you to fall asleep?)

How many nights this week have you had trouble falling asleep?

- 0 – no difficulty falling asleep
- 1 – complains of occasional difficulty falling asleep – i.e. more than 1-2 hours
- 2 – complains of nightly difficulty falling asleep.

7. Insomnia Middle

SCORE_____

During the past week, have you been waking up in the middle of the night?

IF YES: Do you get out of bed? What do you do? (Only to go to the bathroom?)

When you get back in bed, are you able to fall right back asleep?

Have you felt your sleeping has been restless or disturbed some nights?

- 0 – no difficulty
- 1 – complains of being restless and disturbed during the night.
- 2 – waking during the night – any getting out of bed (except to void).

8. Insomnia Late

SCORE_____

What time have you been waking up in the morning for the last time, this past week?

IF EARLY: Is that with an alarm clock, or do you just wake up yourself?

What time do you usually wake up (that is, before you got depressed)?

- 0 – no difficulty
- 1 – waking in early hours of morning but goes back to sleep
- 2 – unable to fall asleep again if gets out of bed

9. Somatic Symptoms – General

SCORE_____

How has your energy been this past week?

Have you been tired all the time?

This week, have you had any backaches, headaches, or muscle aches?

This week, have you felt any heaviness in your limbs, back or head?

- 0 – none
- 1 – heaviness in limbs, back or head. Backache, headache, muscle aches, loss of energy and fatigability
- 2 – any clear-cut symptom

10. Feelings of Guilt

SCORE_____

Have you been especially critical of yourself this past week, feeling that you've done things wrong, let people down?

IF YES: What have your thoughts been?

Have you been feeling guilty about anything you've done or not done?

Have you thought that you've brought (THIS DEPRESSION) on yourself in some way?

Do you feel you're being punished by being sick?

- 0 – absent
- 1 – self-reproach, feels he has let people down
- 2 – ideas of guilt or rumination over past errors or sinful deeds
- 3 – present illness is a punishment. Delusions of guilt
- 4 – hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

11. Suicide

SCORE_____

This past week, have you had any thoughts that life is not worth living, or that you'd be better off dead? What about having thoughts of hurting or even killing yourself?

IF YES: What have you thought about?

Have you actually done anything to hurt yourself?

- 0 – absent
- 1 – feels life is not worth living
- 2 – wishes he were dead or any thoughts of possible death to self
- 3 – suicidal ideas or gesture
- 4 – attempts at suicide

12. Anxiety - Psychic

SCORE_____

Have you been feeling especially tense or irritable this past week?

Have you been worrying about unimportant things, things you wouldn't ordinarily worry about?

IF YES: Like what, for example?

- 0 – no difficulty
- 1 – subjective tension and irritability
- 2 – worrying about minor matters
- 3 – apprehensive attitude apparent in face or speech
- 4 – fears expressed without questioning.

13. Anxiety – Somatic

SCORE_____

(Physiological concomitants of anxiety, such as GI (dry mouth, gas, indigestion, diarrhea, cramps, belching); C-V (heart palpitations, headaches); Respiratory (hyperventilating, sighing); Having to urinate frequently; Sweating).

In this past week, have you had any of these physical symptoms? (READ LIST, PAUSING AFTER EACH FOR REPLY).

How much have these things been bothering you this past week? (How bad have they gotten? How much of the time, or how often, have you had them?)

- 0 – absent
- 1 – mild
- 2 – moderate

- 3 – severe
- 4 – incapacitating

N.B. Don't rate if clearly due to medication (E.g. dry mouth and imipramine)

14. Hypochondriasis

SCORE_____

In the last week, how much have your thoughts been focussed on your physical health or how your body is working (compared to your normal thinking)?

Do you complain much about how you feel physically?

Have you been asking for help for things you could really do yourself? IF YES: Like what, for example? How often has that happened?

- 0 – not present
- 1 – self-absorption (bodily)
- 2 – preoccupation with health
- 3 – frequent complaints, requests for help, etc.
- 4 – hypochondriacal delusions

15. Insight (Rating based on observation)

SCORE_____

- 0 – acknowledges being depressed or ill OR not currently depressed
- 1 – acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
- 2 – denies being ill at all.

16. Retardation (Rating based on observation)

SCORE_____

(Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

- 0 – normal speech and thought
- 1 – slight retardation at interview
- 2 – obvious retardation at interview
- 3 – interview difficult
- 4 – complete stupor

17. Agitation (Rating based on observation)

SCORE_____

- 0 – none

- 1 – fidgetiness
- 2 – playing with hands, hair etc
- 3 – moving about, can't sit still
- 4 – hand-wringing, nail biting, hair-pulling, biting of lips

TOTAL 17-ITEM DEPRESSION SCORE: _____

APPENDIX H - Hamilton Anxiety Scale

Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A)

The purpose of this structured interview is to assist in the reliable assessment of anxiety severity by standardising the method of assessment and providing clear anchor points for the assignment of severity ratings. The interview items and the anchor points are meant to supplement good clinical judgement, not replace it. To ensure full assessment of the domain of inquiry for each item, the interviewer should ask all questions provided. After symptoms for each item are identified, the interviewer must rate severity. For each item, several defining characteristics of each severity score are provided. These defining characteristics are meant as guidelines to aid in the reliable use of the severity scales; they represent examples of the severity levels appropriate to the rating. Severity is defined most readily by the frequency of occurrence, degree of distress and interference associated with the symptom. The number of symptoms present is included in the severity rating only as it impacts on distress and interference. For example, a higher rating may be achieved for a single severe symptom and for several mild or moderate symptoms. Alternatively, several mild symptoms may lead to a moderate rating of severity because of their overall impact on distress.

In addition to the guidelines for each item, the interviewer should note the following conventions for boundary problems:

None to mild boundary: Most questionable cases should be rated as one, as zero is meant to be an anchor point with no symptoms present.

Mild to moderate boundary: Symptoms are endorsed less than fifty percent of the time and cause little or no interference or distress, rate as one. Symptoms are endorsed less than fifty percent of the time and are rated as causing mild to moderate interference or distress, rate as two. Symptoms are endorsed more than fifty percent of the time and are rated as causing mild interference or distress, rate as two.

Moderate to severe boundary: Symptoms are endorsed less than fifty percent of the time and are rated as causing severe interference or distress, rate as three. Symptoms are endorsed more than fifty-percent of the time and are rated as causing moderate to severe interference or distress, but not both, rate as three.

Severe to very severe boundary: Questionable cases should generally be rated as three, ratings of four are reserved for behavioural events clearly identified by the rating anchors.

To elicit the information necessary for assigning severity ratings, the interviewer must access the frequency of occurrence, degree of distress, and degree of interference

associated with symptoms. The following questions are recommended for this assessment:

Have you had *the symptom* every day? IF NO: Have you had *the symptom* more days than not?

How much does *the symptom* bother you?

How much does it interfere with you life?

Starting the interview: Begin the interview with an introduction, describing the scale and its purpose in a way that is relevant for the specific patient and for the specific assessment. For example, for the first administration, one might say, “*As you know, we have diagnosed your condition as an anxiety disorder. We are now going to be asking you a number of questions about different aspects of your anxiety. Together, they allow us to rate as accurately as possible the overall severity of your anxiety state. We will be rating anxiety severity in this way at different points in your treatment in order to decide how much the treatment is helping you.*”

This example is not meant as a script. The interviewer should introduce the scale in a way judged most comfortable for the patient and for her/his own style.

It is assumed that the interviewer has completed a previous diagnostic interview and it familiar with the patient’s general range of symptoms. If this is not true, the interviewer should preface the Hamilton Anxiety Scale by asking for a summary (five to ten minutes) of the patient’s specific worries, disturbing physical symptoms, duration of the syndrome, and its characteristics over time (E.g. Does it tend to wax and wane or has it been persistent since the onset?). The interviewer should also obtain a global statement on distress and impairment during the last week, and the cause of this distress. This information will provide the rate with a background or framework from which to conduct ratings.

Although there are differences between studies, it is assumed that all ratings for the Hamilton Anxiety Rating Scale for patients with Panic Disorder will focus exclusively on times other than panic episodes.

1. Anxious Mood

SCORE: _____

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|--|---|
| What's your mood been like this past week? | 0 – No anxious mood |
| Have you been anxious, nervous? | 1 – Mild worry or anxiety indicated only on questioning; no change in functioning. |
| Have you been worrying? | 2 – Preoccupation with minor events, anxiety on as many days as not. |
| Feeling something bad may happen? | 3 – Near daily episodes of anxiety/worry with disruption of daily activities; daily preoccupation |
| Feeling irritable? | 4 – Nearly constant anxiety; significant role disruption. |

2. Tension

SCORE: _____

- | | |
|---|---|
| Have you been feeling tense? | 0 – No tension |
| Do you startle easily? | 1 – Several days of mild tension or occasional (e.g. 1-2) episodes of exaggerated startle or labile mood |
| Cry easily? | 2 – Muscle tension or fatigue 50% of the time, or repeated (>2) episodes of trembling, exaggerated startle etc. |
| Easily fatigued? | 3 – Near daily muscle tension, fatigue and/or restlessness >75% of the time or persistent, disruptive symptoms. |
| Have you been trembling or feeling restless or unable to relax? | 4 – Constant tension, restlessness, agitation, unable to relax in the interview. |

3. Fears

SCORE: _____

Have you been feeling fearful (phobic) of situations or events?

For example, have you been afraid of the dark?

Of strangers?

Of being left alone?

Of animals?

Of being caught in traffic?

Of crowds?

Other fears?

0 – No fears

1 – Mild phobic concerns that do not cause significant distress or disrupt functioning.

2 – Fears lead to distress or avoidance on one or more occasions.

3 – Fears are an object of concern on a near daily basis (75%); patient may need to be accompanied by others to a fearful event.

4 – Fears or avoidance that markedly effect function. Patient may avoid multiple situations even if accompanies; extensive agoraphobia.

4. Insomnia

SCORE: _____

How has your sleeping been this week?

Any difficulties falling asleep?

Any problems with waking during the night? Waking early and not being able to return to sleep?

Do you feel rested in the morning?

Do you have disturbing dreams or nightmares?

0 – No sleep disturbance

1 – Mildly disrupted sleep (e.g. one to two nights of difficulties falling asleep or nightmares).

2 – Several episodes of sleep disturbance that is regular but not persistent (e.g. over one-half hour falling asleep, nightmares or excessive AM fatigue).

3 – Persistent sleep disruption (more days than nor) characterised by difficulty falling (e.g. over one hour) or staying asleep, restlessness, unsatisfying sleep or frequent nightmares, or fatigue.

4 – Nightly difficulties with sleep onset or maintenance, or daily severe fatigue on waking in the AM.

5. Intellectual

SCORE: _____

Have you had any trouble concentrating or remembering things?

0 – No difficulties

1 – Infrequent episodes of forgetfulness or difficulty concentrating that are not distressing to the patient.

2 – Recurrent episodes of forgetfulness or difficulty concentrating, or episodes of sufficient intensity to cause the patient recurrent concern.

3 – Persistent concentration or memory impairment interferes with daily tasks.

4 – Significant role impairment due to concentration difficulties.

6. Depressed Mood

SCORE: _____

Have you been feeling depressed?

0 – No depression

Have you lost interest in things?

1 – Occasional or mild blue or sad mood, or reports of decreased enjoyment of activities

Do you get pleasure from friends or hobbies?

2 – Sad or blue mood or disinterest 50% of the time, mood does not generally interfere with functioning.

3 – Persistent depressed mood or loss of pleasure, mood is significantly distressing to the patient or may be evident to others.

4 – Daily evidence of severe depression with significant role impairment.

7. Somatic Complaints: Muscular

SCORE: _____

Have you been experiencing aches, pains, or stiffness in your muscles?

Have you experienced muscle twitching or sudden muscle jerks?

Have you been grinding your teeth?

Have you had an unsteady voice?

0 – No muscular symptoms

1 – Infrequent presence of one or two symptoms, no significant distress.

2 – Mild distress over several symptoms or moderate distress over a single symptom.

3 – Symptoms occur on more days than not, symptoms are associated with moderate to severe distress and/or regular attempts at symptom control by limiting activities or taking medications.

4 – Daily or near daily episodes of symptoms that cause the patient significant distress and lead to restriction of activities or repeated events for medical attention.

8. Somatic Complaints: Sensory

SCORE: _____

Have you been experiencing ringing in your ears, blurred vision, hot or cold flashes, feelings of weakness or prickling sensations?

Has this occurred at times other than during a panic attack?

0 – No symptoms

1 – Infrequent presence of one or two symptoms, no significant distress.

2 – Mild distress over several symptoms or moderate distress over a single symptom.

3 – Symptoms occur on more days than not, symptoms are associated with moderate to severe distress and/or regular attempts at symptom control by limiting activities or taking medications.

4 – Daily or near daily episodes of symptoms that cause the patient significant distress and lead to restriction of activities or repeated visits for medical attention.

9. Cardiovascular problems

SCORE: _____

Have you had episode of a racing, skipping, or pounding heart?

How about pain in your chest or fainting feelings?

(Has this occurred at times other than during a panic attack?)

0 – No symptoms

1 – Infrequent presence of one or two symptoms, no significant distress.

2 – Mild distress over several symptoms or moderate distress over a single symptom.

3 – Symptoms occur on more days than not, symptoms are associated with moderate to severe distress and/or regular attempts at symptom control by limiting activities or taking medications.

4 – Daily or near daily episodes of symptoms that cause the patient significant distress and lead to restriction of activities or repeated visits for medical attention.

10. Respiratory Symptoms

SCORE: _____

Have you been having trouble with your breathing?

For example, pressure or constriction in your chest, choking feelings, sighing or feeling like you can't catch your breath?

Has this occurred at times other than during a panic attack?

0 – No symptoms

1 – Infrequent presence of one or two symptoms, no significant distress.

2 – Mild distress over several symptoms or moderate distress over a single symptom.

3 – Symptoms occur on more days than not, symptoms are associated with moderate to severe distress and/or regular attempts at symptom control by limiting activities or taking medications.

4 – Daily or near daily episodes of symptoms that cause the patient significant distress and lead to restriction of activities or repeated visits for medical attention.

11. Gastrointestinal Symptoms

SCORE: _____

Have you had any difficulties with stomach pain or discomfort?

Nausea or vomiting?

Burning or rumbling in your stomach?

Heartburn?

Loose bowels?

Constipation?

Sinking feeling in your stomach?

Has this occurred at times other than during a panic attack?

0 – No symptoms

1 – Infrequent and minor episodes of gastric discomfort, constipation, or loosening of bowels, fleeting nausea.

2 – An episode of vomiting or recurrent episodes of abdominal pain, loosening of bowels, difficulty swallowing, etc.

3 – Symptoms more days than not that are very bothersome to the patient or lead to concerns over eating, bathroom availability, or use of medication.

4 – Daily or near daily episodes of symptoms that cause the patient significant distress and lead to restriction of activities or repeated visits for medical attention.

12. Genitourinary Symptoms

SCORE: _____

Have you been experiencing urinary difficulties? For example, have you had to urinate more frequently than usual?

Have you had more urgency to urinate?

Have you had decreased sexual interest?

FOR WOMEN: Have your periods been regular? Have you experienced a change in your ability to orgasm?

FOR MEN: Have you had trouble maintaining an erection? Ejaculating prematurely?

0 – No symptoms

1 – Infrequent and minor episodes of urinary symptoms or mild changes in sexual interest.

2 – Urinary symptoms several days during the week, occasional difficulties with sexual function.

3 – Urinary or sexual symptoms more days than not, amenorrhea.

4 – Daily urinary or sexual symptoms that lead to distress and medical care seeking.

13. Autonomic Symptoms

SCORE: _____

Have you been experiencing flushing in your face?

Getting pale?

Light-headedness?

Have you been having tension headaches?

Have you felt the hair rise on your arms, the back of your neck or head, as though something had frightened you?

Has this occurred at times other than during a panic attack?

0 – No symptoms

1 – Mild symptoms occurring infrequently.

2 – Symptoms occurred several times during the week and were bothersome.

3 – Near daily symptoms with distress or embarrassment about the symptoms.

4 – Daily symptoms that are a focus of distress and impair function (e.g. daily headaches or light-headedness leading to limitation of activities).

14. Behaviour at Interview

SCORE: _____

E.g. fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respirations, facial pallor, frequent swallowing, etc.

0 – No apparent symptoms

1 – Presence of one or two symptoms to a mild degree.

2 – Presence of several symptoms or mild intensity or one symptom of moderate intensity.

3 – Persistent symptoms throughout the interview.

4 – Agitation, hyperventilation, difficulty completing the interview.